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HORMONES IN CANCER-RELATED BIOLOGY

Non-Steroid Hormones

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CHARACTERIZATION OF NON-STEROID HORMONES IN EXPERIMENTAL AND IN VITRO SYSTEMS

1. SECRETION OF LH, FSH AND PRL SHOWN BY CELL CULTURE AND IMMUNOCYTOCHEMISTRY OF HUMAN FUNCTIONLESS PITUITARY ADENOMAS.

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Clin Endocrinol (Oxf); 15(2):103-112 1981

Hormone secretion by ten functionless human pituitary adenomas in cell culture has been measured, and compared with tissue immunocytochemistry and electron microscopy, as well

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as results with a normal pituitary. Patients presented following routine x-ray and had no clinical or biochemical en docrine abnormality apart from one male with raised serum FSH and PRL, normal LH, and low testosterone. Of the ten adenomas, nine secreted both LH and FSH in cell culture and five of these also secreted PRL, one did not secrete any anterior pituitary hormones (ACTH was not measured). No GH or TSH was detectable in the cultures of the nine LH/FSH secretors excluding the possibility of contamination by normal anterior pituitary. The normal pituitary cells secreted all anterior pituitary hormones; the amounts of FSH/LH being comparable with those of the adenomas. Immunostaining confirmed the cell culture results and showed the adenoma FSH/LH cells to be scattered singly or in small groups of two to five cells with both hormones usually being in the same cell. PRL where found was in separate cells. Hormone granules were small (50-160 nm), round or irregular and scattered in the cytoplasm of rounded cells of low secretory activity. The negatively staining cells were not different ultrastructurally to those staining positively. It is concluded that a significant proportion of functionless pituitary adenomas have detectable low levels of LH/FSH secretion often accompanied by PRL when examined by cell culture of immunocytochemistry. Although these adenomas were endocrinologically quiescent activity could have been masked because of postmenopausal secretion and one male probably had an FSH-secreting adenoma. (Author abstract) (32 Refs)

2. MULTIPLE FORMS OF HUMAN TUMOR CALCITONIN DEMONSTRATED BY DENATURING POLYACRYLAMIDE GEL ELECTROPHORESIS AND LECTIN AFFINITY CHROMATOGRAPHY.

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J Clin Endocrinol Metab; 53(3):489-497 1981

The mol wt forms of immunoreactive calcitonin in human tumors have been studied using two sodium dodecyl sulfate polyacrylamide gel electrophoretic systems. Under denaturing conditions, which produce monomer peptides, it has been possible to document further the size heterogeneity of this immunoreactivity. Small mol wt forms (native size human calcitonin of 3,600 daltons and immunoreactive peptides of 4,000-6,000 daltons) predominated in extracts of four medullary thyroid carcinomas. Smaller amounts of larger mol wt forms (8,000-22,000 daltons) were detected. In one medullary thyroid carcinoma and in an extract of small (oat) cell lung carcinoma, the higher mol wt forms predominated, with the greatest amount of immunoreactivity found in 12,000-and 10,000-dalton peptides. Evidence has been obtained that all of the tumors studied contain a component of immunoreactive calcitonin that binds to lectins immobilized on agarose. Five to 20% of the total immunoreactive material from the medullary thyroid carcinomas and from human small (oat) cell lung carcinoma bound to columns of agarose-bound Concanavalin A and/or wheat germ agglutinin. The conditions of binding and elution with specific sugars strongly suggest that this lectin-bound immunoreactive calcitonin may contain mannose and N-acetylglucosamine residues. Gel electrophoresis of the carbohydrate-eluted material showed that the lectin-bound forms comprise a portion of each of the several mol wt classes of immunoreactive calcitonin moieties identified. These studies indicate further that human tumors contain different sizes of calcitonin immunoreactivity and that the ratios among these forms may vary among different neoplasms. The fact that some calcitonin forms may contain carbohydrate moieties is another potential determinant for the heterogeneity of the circulating immunoreactive calcitonin in patients with medullary thyroid carcinoma or small (oat) cell lung cancer. (Author abstract) (40 Refs)

3. A HUMAN PARATHYROID CARCINOMA THAT PRODUCES PARATHYROID HORMONE: LONG TERM MAINTENANCE IN TISSUE CULTURE.

Pattillo RA, Ruckert AC, Wilson SD, Hussa RO, Gray RW, Lemann J

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J Clin Endocrinol Metab; 53(3):641-644 1981

Parathyroid carcinoma cells from a pulmonary metastasis of a patient with a serum Ca of 17 mg/dl and an immunoreactive parathyroid hormone (PTH) of 6.4 ng eq bovine (b) PTH/ml (normal 40-400 pg/ml) have been maintained in tissue culture for more than 2 1/2 yr. The cells secrete PTH into the culture media that (1) during immunoassay dilutes in parallel to human hyperparathyroid serum, (2) has a mol wt similar to intact highly purified bPTH, and (3) stimulates bone resorption in a manner that is equivalent and additive to synthetic bPTH-(1-34). (Author abstract) (12 Refs)

4. NEUROHORMONAL PEPTIDE IMMUNOREACTIVE CELLS IN MUCINOUS CYSTADENOMAS AND CYSTADENOCARCINOMAS OF THE OVARY.

Sporrong B, Alumets J, Clase L, Falkmer S, Hakanson R, Ljungberg O, Sundler F

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Virchows Arch [Pathol Anat]; 392(3):271-280 1981

In 144 benign mucinous cystadenomas of the ovary, 33 mucinous cystadenomas of borderline malignancy and 64 mucinous cystadenocarcinomas, the incidence of tumors containing argyrophil (and probably endocrine cells) was 18%, 33%, and 53%, respectively. The results of a semiquantitative assessment of the number of argyrophil cells in each individual tumor indicates that the greatest numbers occurred in the cystadenocarcinomas. As, however, the tumor cell density was larger in the cystadenocarcinomas than in the cystadenomas, and as the argyrophil cells often had a patchy distribution in the tumor epithelium, the incidence figures are unreliable. In addition, visualization of the argyrophil cells depends on an ade quate fixation which is difficult to achieve in the routine processing of large tumor specimens. Many argyrophil cells in the cystadenocarcinomas displayed immunoreactivity with antisera raised against gastro-entero-pancreatic (GEP) neurohormonal peptides. In 10 such tumors immunohistochemical evidence was obtained for the presence of the following neurohormonal peptides in the tumor cells: somatostatin, glucagon, gastrin/CCK, neurotensin, and enkephalin. Four of these 10 cystadenocarcinomas were multihormonal, in that 3 contained two cell populations storing GEP neurohormonal peptides, and 1 tumor even three such populations. In the benign cystadenomas, however, no immunoreactive tumor cells were found. In those of borderline type, only two harbored immunoreactive cells. In both cases the tumor cells stored gastrin/CCK. The general appearance of the epithelium in the mucinous tumors - a continuous single-cell layer of mucin-producing cells intermingled with argyrophil cells of open type - and the spectrum of neurohormonal peptides observed, indicate an origin from the foregut endoderm. (Author abstract) (29 Refs)

5. IMMUNOCYTOCHEMISTRY AND ELECTRON MICROSCOPY OF AN ARGENTAFFIN ENDOCRINE TUMOUR OF THE PANCREAS.

Wilander E, El-Salhy M, Willen R, Grimelius L
Dept. Pathology, Univ. Uppsala, P.O. Box 533, S-751 22, Uppsala, Sweden
Virchows Arch [Pathol Anat]; 392(3):263-269 1981

An endocrine pancreatic tumor that had not caused any endocrine symptoms was examined by histological, immunocytochemical and electron microscopic techniques. The majority of the tumor cells were argentaffin and contained secretory granules of the enterochromaffin cell type. Immunocytochemically a minority of tumor cells reacted to antisera against beta-endorphin, met- and leu-enkephalin, gastrin, somatostatin and ACTH. The tumor was thus multihormonal, and appeared to be more closely related to the classic Carcinoid tumors of the mid-gut than to most pancreatic endocrine tumors. (Author abstract) (20 Refs)

6. SPECIFIC ENZYME IMMUNOASSAY FOR HUMAN CHORIONIC GONADOTROPHIN.

Sekiya T, Furuhashi Y, Goto S, Kaseki S, Tomoda Y, Kato K
Dept. Obstetrics and Gynaecology, Nagoya Univ., Sch. Medicine, Nagoya, Japan
Acta Endocrinol (Kbh); 97(4):562-568 1981

A sandwich-type enzyme immunoassay system specific for human chorionic gonadotrophin (hCG) was prepared with the antibody Fab'-beta-D-galactosidase complex and the antibody F(ab')2-immobilized silicone rubber solid phase by using a purified antibody to beta subunit of hCG (hCGbeta). The assay system cross-reacted less than 4% with human luteinizing hormone (hLH) and human follicular stimulating hormone (hFSH), and proved to be highly sensitive with hCG measurable at levels as low as 0.3 mIU per assay tube. Using 50 ul of serum sample, 6-600 mIU/ml of hCG in serum could be determined specifically with the same degr ee of precision as in radioimmunoassay but without sample interference with the assay. The coefficients of variation within-run and between-run were 8.6-8.9%, and 4.9-10.7%, respectively. Values obtained with the enzyme immunoassay correlated well with those of radioimmunoassay (r = 0.98, slope = 0.94, y-intercept = 10.2 mIU/ml for 75 serum samples). Results of the immunoassay of hCG levels in serial samples of serum from healthy women and patients with choriocarcinoma show that this method is useful in the clinical diagnosis of trophoblastic disease. (Author abstract) (11 Refs)

7. TISSUE LEVELS OF MONOAMINES AND MONOAMINE METABOLIZING ENZYMES IN MEDULLARY CARCINOMA AND OTHER THYROID DISEASES.

Feldman JM, Wells SA
Box 2963, Duke Univ. Medical Center, Durham, NC, 27710
Am J Med Sci; 282(1):34-40 1981

Medullary carcinoma of the thyroid (MCT) originates from the parafollicular cells of the thyroid. Many MCT contain large quantities of histaminase. There are some histologic and biochemical suggestions that MCT also may contain increased quantities of monoamines such as serotonin and norepinephrine (NE). This report compares the levels of monoamines and monoamine metabolizing enzymes in nine consecutive MCT removed in our medical center with the levels in normal thyroid tissue, follicular adenomas of the thyroid, colloid nodules of the thyroid, and chronic (Hashimoto's) thyroiditis tissue. There was no significant difference in the serotonin, NE, and dopamine concentrations in most MCT and normal thyroid tissues. Although the serotonin concentration of follicular adenomas and colloid nodules did not differ from that of normal thyroid tissue, the NE concentration of colloid nodules was decreased. The monoamine oxidase (MAO) and catechol-o-methyltransferase (COMT) activity of MCT and colloid nodules did not differ from normal thyroid tissue. The MAO activity of follicular adenomas was significantly higher than the MAO activity of normal thyroid tissue when the enzyme activity was expressed either per unit protein or per unit DNA. The COMT activity of follicular adenomas was significantly higher than the COMT activity of normal thyroid tissue when expressed per unit protein, but was not significantly different when expressed per unit DNA. One of the nine MCT we evaluated had increased levels of NE, dopamine, MAO and COMT. In addition, it contained increased amounts of epinephrine and the epinephrine synthesizing enzyme phenylethanolamine-N-methyltransferase. We conclude that the levels of monoamines and monoamine metabolizing enzymes are not increased in most MCT. However, the activity of MAO is increased in other neoplasms such as follicular adenoma. (Author abstract) (31 Refs)

CLINICAL, DIAGNOSTIC AND PROGNOSTIC STUDIES

8. RAPID CHANGES OF PROLACTINOMA VOLUME AFTER WITHDRAWAL AND REINSTITUTION OF BROMO CRIPTINE.

Thorner MO, Perryman RL, Rogol AD, Conway BP, MacLeod RM, Login IS, Morris JL
Dept. Internal Medicine, Univ. Virginia Sch. Medicine, Charlottesville, VA, 22908
J Clin Endocrinol Metab; 53(3):480-483 1981

Medical therapy of prolactinomas with bromocriptine has been demonstrated to reduce serum PRL levels to normal and also to reduce the size of such tumors. This size reduction may occur very rapidly. It is widely recognized that PRL levels rise again after withdrawal of bromocriptine therapy. We now describe the effects of drug withdrawal and reinstitution on tumor size in two young men harboring large prolactinomas. Bromocriptine had been extremely successful in lowering serum PRL levels by more than 80%, as well as reducing tumor size. After 12 mo of therapy bromocriptine was withdrawn. Within 48 hr PRL levels had started to rise, reaching 2,580 ng/ml at 13 days off therapy and 1,040 ng/ml at 4 wk off therapy in patients 1 and 2, respectively. At 13 days bitemporal hemianopsia recurred in patient 1, and this was associated with radiographic demonstration of expansion in the pituitary mass from a partially empty pituitary fossa to a large 12-mm suprasellar extension. The second patient remained asymptomatic,, but his tumor also reexpanded after withdrawal of bromocriptine. Bromocriptine (2.5 mg tid) was reinstituted in both cases and resulted in a rapid fall in serum PRL and reduction of tumor size in both patients; patient 1 had improvement in headaches at 24 hr, vision at 3 days, and restoration of visual fields to normal at 6 mo. Bromocriptine therapy is successful in reducing tumor size and lowering PRL levels with return of normal gonadal function. Patients with large prolactinomas treated with bromocriptine alone should be withdrawn from therapy very cautiously to avoid reexpansion of their tumor. (Author abstract) (18 Refs)

9. PROLACTIN AND PLACENTAL HORMONES DURING PREGNANCY IN PROLACTINOMAS.

Batrinos ML, Panitsa-Faflia C, Anapliotou M, Pitoulis S
Dept. Endocrinology, Alexandra Hosp., Athens (Goudi 609), Greece
Int J Fertil; 26(2):77-85 1981

Levels of prolactin (PRL), estradiol, estriol, progesterone, placental lactogen, and chorionic gonadotropin were measured during pregnancy and early postpartum in three patients with prolactinoma. Pregnancy had been achieved by (1) bromocriptine treatment, (2) irradiation of the pituitary, or (3) human gonadotropin treatment after excision of the tumor. Case 1 showed high pretreatment levels of PRL, which were reduced by the bromocriptine treatment. PRL again climbed to pretreatment level in the 2nd mo of pregnancy, followed by another increase after the 30th wk. PRL level dropped just before labor, which occurred 1 wk after a severe headache and dizziness. It further declined postpartum. PRL in case 2 was reduce d, but not to normal levels, by treatment; it remained slightly raised during pregnancy. PRL in case 3 remained in the low normal range throughout pregnancy and early postpartum. Patients 2 and 3 gave birth to normal twins. Placental hormones were normal in all cases. Estradiol and progesterone reached higher levels late in pregnancy in the cases with twins. Agalactia occurred in all three cases. Results indicate that PRL measurements reflect changes in prolactinomas, maternal hyperprolactinemia or failure of PRL to increase during pregnancy does not affect placental hormone secretion or amniotic fluid PRL, and hyperprolactinemia during pregnancy is of maternal pituitary origin. (30 Refs)

10. ABNORMAL REGULATION OF PROLACTIN SECRETION AFTER SUCCESSFUL SURGERY FOR PROLACTIN-SECRETING PITUITARY TUMOURS.

Schlechte JA, Sherman BM
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Clin Endocrinol (Oxf); 15(2):165-174 1981

Patients with prolactin-secreting pituitary tumors have a diminished prolactin (PRL) response after administration of a variety of stimulatory agents, including thyrotropin-releasing hormone (TRH), chlorpromazine (CPZ) and insulin-induced hypoglycemia. We examined responses to these agents in 67 women with PRL-secreting tumors before and after transsphenoidal surgery. Twenty-nine of the women were cured as defined by restoration of normal serum PRL concentrations and resumption of regular menses. One yr following transsphenoidal surgery, patients with normal PRL concentrations and regular menses had normal PRL responses to TRH, while the responses to CPZ and insulin hypoglycemia were not improved. The reversible impairment of PRL response to TRH reflects suppressed function of normal PRL-secreting cells, and the persistence of abnormal PRL responses to provocative stimuli after successful tumor removal may reflect some fundamental defect in the regulation of PRL secretion in patients with PRL-secreting adenomas. When growth hormone (GH) reserve after insulin hypoglycemia was represented as the mean absolute increment above the basal concentration and compared with normal subjects, women with PRL-secreting tumors had a diminished response that returned to normal after successful surgery. This reversible impairment of GH secretion is not adequately reflected by standard criteria for GH response and suggests that PRL may have a role in the regulation of GH secretion. (Author abstract) (46 Refs)

11. PROLACTIN: PHYSIOLOGY AND PHYSIOPATHOLOGY.

Cowden EA, Friesen HG
Departement de Physiologie, Faculte de Medecine, Universite de Montreal, Montreal, Quebec, Canada
Neurochirurgie; 27(Suppl1):9-17 1981

Recent research on the physiology and physiopathology of prolactin (PRL) is discussed. Topics considered include the physiologic control of the PRL secretion, clinical aspects PRL secre tion, and the research on the nonlactogenic role of PRL (exogenous administration of PRL, metabolic disorders in hyperprolactinemia, and PRL in pathologic conditions). (99 Refs) (In FRE)

12. PROLACTIN LEVEL AND ITS REACTION TO THYROLIBERIN IN THYROID DISEASES.

Vakulenko AD, Niiazova ZhM, Simakova GM
Inst. Medical Radiology, Obninsk, USSR
Probl Endokrinol (Mosk); 27(4):6-10 1981

Prolactin (PL) level and its reaction to thyroliberin (thyrotropin releasing hormone: TRH) was studied in 136 patients with various thyroid diseases and in 15 healthy controls. Significant decrease of the basal and stimulated PL levels were recorded in the patients with euthyroid goiter and especially in the patients with thyroid carcinoma. It was recommended to use a TRH test for the differential diagnosis between the euthyroid nodular goiter and other nodular thyroid lesions. (20 Refs) (In RUS)

13. INAPPROPRIATE SECRETION OF THYROID-STIMULATING HORMONE.

Weintraub BD, Gershengorn MC, Kourides IA, Fein H
NIH, Building 10, Room 8N315, Bethesda, MD, 20205
Ann Intern Med; 95(3):339-351 1981

Recent studies have provided major new insights into the syndromes of inappropriate secretion of thyroid-stimulating hormone (TSH), a heterogeneous group of disorders in which patients show inappropriately elevated levels of serum immunoactive TSH in the presence of elevated free thyroid hormone levels. Certain of these patients appear to have a non-neoplastic disorder associated with variable degrees of pituitary and peripheral resistance to the action of thyroid hormone, whereas others harbor a tumor of pituitary thyrotropic cells. Measurement of free serum alpha subunit has proved valuable in differentiating these disorders, showing normal alpha concentration and alpha-to-TSH ratios in the non-neoplastic and highly elevated values in the neoplastic disorders. All these syndromes appear unrelated to Graves' disease because thyroid-binding and thyroid-stimulating antibodies are usually absent. Some of these patients also have abnormal metabolism of thyroid hormones. Although the pathogenesis of these syndromes remains to be elucidated, increased recognition and study of these patients should provide fundamental insights into the regulation of TSH secretion as well as the action of thyroid hormone. (Author abstract) (85 Refs)

14. BREAST CANCER AND TRH - RESPONSE.

Kohler AH, Kuhnel W, Kilz F
Bezirkskrankenhaus Cottbus, Radiologische Klinik, Thiemstrasse 111, 7500 Cottbus, E. Germany
Arch Geschwulstforsch; 51(3):273-278 1981

The hypothesis that hypothyroidism may be related to breast cancer was tested. Thiry-seven patients with histologically-confirmed breast cancer were compared with 30 healthy controls. All patients were postmenopausal, with a median age of 62.3 yr. They were examined 10 days after radical mastectomy. Assays measured serum creatinine, triiodothyronine binding capacity, and thyroid stimulating hormone (TSH). The effect of thyrotropin releasing hormone (TRH) on TSH levels was measured. After TRH stimulation (200 ug iv) the mean TSH level was 10.82 uIU/ml in the patient group and 12.70 uIU/ml among controls. The difference was not statistically significant. The results did not support a relationship between hypothyroidism and breast cancer. (35 Refs)

15. ENDOCRINE MANIFESTATIONS OF CANCER AND ITS TREATMENT.

Shalet SM
Christie Hosp., Manchester, England
Practitioner; 225(1356):829,831,833,835,836 1981

Endocrine manifestations of cancer may be due to ectopic secretion in non-endocrine tissue and also may be due to secretion of a 'foreign' hormone from a tumor of an endocrine gland. Syndromes resulting from ectopic hormone secretion of various tumors and the appropriate treatments are discussed. Presented are ectopic ACTH secretion, ectopic anti-diuretic hormone production, disturbances resulting in hypercalcemia, ectopic human chorionic gonadotropin secretion, calcitonin production, erythrocytosis associated with malignant disease, and implications of such ectopic hormone secretion. A second section outlines the endocrine consequences of the treatment of cancer. It is now known that hypopituitarism may be caused by external radiation not directly involving the hypothalamic-pituitary region. Deficiency of thyrotropin, ACTH and gonadotropins may also result from radiation to the hypothalamic-pituitary axis. Radiation-induced dysfunction of the thyroid has been related to therapeutic radiation for various conditions. An increased incidence of hyperparathyroidism has been reported in patients with previous irradiation of the neck. Gonadal function in both male and female may be induced by radiation and cytotoxic agents. (6 Refs)

16. TUMOUR MARKERS: THEIR ROLE IN CLINICAL MEDICINE.

Dearnaley DP, Coombes RC
Clinical Oncology Unit, Ledwig Inst. Cancer Res. (London Branch), Royal Marsden Hosp., Sutton, Surrey, England
Practitioner; 225(1356):839-841,843-844,846-849 1981

Biochemical tumor markers currently used in diagnosis and monitoring responses to treatment are human chorionic gonadotropin (HCG) in trophoblastic tumors; beta subunit HCG and alpha-fetoprotein (AFP) in testicular tumors; AFP (if the initial titer is very high) in hepatomas; acid phosphatase in prostatic cancer; catecholamines in neuroectodermal tumors; and calcitonin in medullary carcinoma of the thyroid. Carcinoembryonic antigen (CEA) assays are useful for monitoring responses to treatment in .patients with colorectal cancer, but cannot be used in diagnosis. Certain lung tumors (especially oat cell carcinomas) secrete ectopic ACTH, antidiuretic hormone, and/or calcitonin. These ectopic hormones may also be present in patients with chronic obstructive pulmonary disease, but the ectopic hormones associated with lung cancer are often of abnormally high mol wt. Assays for these high-mol wt hormones may be useful for monitoring responses to therapy. Adenocarcinomas and squamous cell carcinomas of the lung may produce CEA, alkaline phosphatase, and gamma-glutamyl transpeptidase. However, elevated CEA levels are present in smokers and patients with many non-neoplastic and inflammatory diseases, and the enzymes are not tumor-specific. At present, the role of biochemical markers in the management of the common solid tumors is rather limited. The use of tumor markers in breast and lung cancer must await further research. Monoclonal antibody technology should soon provide satisfactory antibodies for immunolocalization and immunocytochemistry studies in breast cancer patients. (12 Refs)

17. HORMONES: NEW POTENTIAL FOR TUMOR MARKERS.

Braunstein GD
Div. Endocrinology, Cedars-Sinai Medical Center, Los Angeles, CA
Diagn Med; 4(4):59-60,62,64-66,68,72,74 1981

Very useful diagnostic tests exist for functional tumors of the endocrine glands that measure the abnormal hormonal secretions. Medullary carcinoma of the thyroid is derived from the calcitonin-producing C-cells and secretes excessive amounts of calcitonin; a provocative test for calcitonin secretion coupled with serum calcitonin measurements is useful in screening and diagnosis. Pheochromocytomas are best detected by tests for urinary excretion of catecholamines or their metabolites. Carcinoid tumors, which arise from enterochromaffin cells in many areas of the body, actively produce vasoactive peptides such as serotonin, histamine, and kallikrein and secrete biogenic amines; the most useful test for them is measurement of the urinary 5-hydroxyindoleacetic acid. Islet cell tumors may be associated with the overproduction of numerous hormones, including insulin, glucagon, gastrin, and somatostatin, and numerous tests exist to measure these abnormalities. Adrenocortical carcinomas may secrete excessive amounts of glucocorticoids, mineralocorticoids, androgens, or estrogens, all of which may be measured directly or indirectly (by their metabolites) in serum and/or urine. Testicular tumors may be germ-cell tumors that secrete chorionic gonadotropin or Leydig-cell tumors that secrete estrogens or androgens; they may also be accompanied by elevated levels of alpha-fetoprotein; all of these substances are amenable to assay. Most ovarian tumors do not secrete abnormal amounts of hormones, but may overproduce estrogens, androgens, and progestogens. Ectopic production of virtually every protein or polypeptide hormone is common but extremely variable so that tests for such production are not very cost-effective as screening procedures, although serial hormone measurements in these cases can be useful as a clinical monitor. (24 Refs)

18. INCREASE OF BETA-ENDORPHIN IN CEREBROSPINAL FLUID AFTER REMOVAL OF ACTH-SECRETING PITUITARY ADENOMAS.

Furui T, Kageyama N, Kuwayama A, Nakao K, Fukushima M
Dept. Neurosurgery, Nagoya Univ. Sch. Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466, Japan
Pain; 11(1):127-132 1981

Beta-endorphin (BEN) and met-enkephalin (MEK) were measured in cerebrospinal fluid (CSF) before and after removal of an ACTH-secreting pituitary adenoma in four patients with Cushing's disease. BEN was measured by radioimmunoassay, MEK was measured by radio-receptor assay, and ACTH in the plasma was measured by radioimmunoassay. After tumor resection, the ACTH level in plasma markedly decreased from 82.6 +-22.7 picog/ml to 16.7 +-4.1 picog/ml. The immunoreactive BEN level in CSF was significantly elevated after resection from 32.0 +-4.5 picog/ml to 61.8 +-10.7 picog/ml. In three cases, MEK-like substance level in CSF decreased after tumor resection, but the alteration was not statistically significant. These results suggest the possibility that BEN participates in the analgesic effect of hypophysectomy. (29 Refs)

19. MULTIPLE PLASMA STEROID RESPONSES TO GRADED ACTH INFUSIONS IN PATIENTS WITH PRIMARY ALDOSTERONISM.

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J Lab Clin Med; 98(3):364-373 1981

We measured the simultaneous responses of eight plasma steroids to the infusion of alpha 1-24 ACTH at incremental rates of 12.5 to 200 mIU/30 min in seven patients with primary aldosteronism (5 with adenomas, 2 with adrenal hyperplasia) and in 10 normal controls studied on regular sodium intakes and while supine. Patients with primary aldosteronism from adenomas had relatively higher concentrations (p less than 0.05) of aldosterone, 18 OH-B, corticosterone, and DOC than the two with hyperplasia and, save corticosterone, above the range of the normal controls. We found inconsistent differences in plasma progesterone, 17-hydroxyprogesterone, deoxycortisol, and cortisol. These findings suggest that the intermediate steps in aldosterone biosynthesis are hypersensitive to physiologic amounts of ACTH in patients with aldosterone-producing adenomas. Plasma levels of steroids distal to progesterone, ie, DOC, corticosterone, 18 OH-B, and aldosterone, are relatively higher after small amounts of ACTH in patients with adenomas than in normal subjects or those with adrenal hyperplasia. (Author abstract) (29 Refs)

20. SERUM THYROGLOBULIN IN THYROID CANCER.

Black EG, Gimlette TM, Maisey MN, Cassoni A, Harmer CL, Oates GD, Hoffenberg R

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Lancet; 2(8244):443-445 1981

Serum thyroglobulin (Tg) was measured in 274 patients with differentiated thyroid cancer; 266 had previous thyroidectomy, which had been followed by ablative iodine-131 in 183 cases. Neither the presence nor the titer of anti-Tg antibodies appeared to effect Tg assays. Serum Tg reflected the presence or absence of cancer in 83% of 164 patients not receiving thyroxine (T4). This concordance improved to 97.5% in 158 patients tested while receiving T4. Thirty four patients in remission were tested both on and off T4 therapy; in all these patients the Tg level when receiving T4 was less than 5 ug/l. In 19 of 21 patients with cancer T4 treatment did not suppress Tg. Serum Tg thus provides an excellent marker for the presence or absence of thyroid cancer in patients taking T4, even if anti-Tg antibodies are present. It is proposed that monitoring of patients by assay of serum Tg should supplant routine assessment by radioactive-iodine scans of the neck or whole body. (Author abstract) (14 Refs)

21. HYPERCALCAEMIA DUE TO DIHYDROTACHYSTEROL TREATMENT IN PATIENTS WITH HYPOTHYROIDISM AFTER THYROIDECTOMY.

Lamberg BA, Tikkanen MJ

Endocrine Res. Lab., Univ. Helsinki, Helsinki, Finland

Br Med J; 283(6289):461-462 1981

Hypercalcemia is a recognized complication of hypothyroidism. We describe three patients who developed hypercalcemia after thyroidectomy when thyroid supplements were discontinued. They were treated with thyroxine, dihydrotachysterol, and calcium after operation, and in all three cases serum calcium concentrations remained constant during combined treatment. Thyroxine treatment was discontinued several wk before a radioiodine scan was performed; dihydrotachysterol and calcium were continued throughout. Serum calcium concentrations rose to hypercalcemic levels in all cases. Elimination of dihydrotachysterol from plasma may be delayed in hypothyroidism, resulting in hypervitaminosis D. It is advisable to reduce the dose of dihydrotachysterol and to check serum calcium concentrations regularly in patients whose thyroid treatment is interrupted. (Author abstract) (4 Refs)

22. LOW VALUE TRIIODOTHYRONINE FOR BLOOD OF TUMOR-BEARING PATIENTS AND RATS (MEETING ABSTRACT).

Miki T, Azukizawa M, Kumahara Y, Okada A, Hasegawa J, Kim M, Miyai K

Fourth Dept. Internal Medicine, Medical Sch., Osaka Univ., Kita-ku, Osaka 530, Japan

Proceedings of the 17th Annual Meeting of the Japan Society of Clinical Biochemistry and Metabolism held in Osaka, 24-25 January, 1980. The Japan Society of Clinical Biochemistry and Metabolism, Tokyo 113, Japan, 277 pp., 1981.

The concentration of tetraiodothyronine (T4), triiodothyronine (T3), reverse triiodothyronine (rT3), thyroid-stimulating hormone (TSH), thyroxine binding globulin (TBG) and total pr otein (TP) in the plasma of 10 tumor-bearing patients was measured before and after the administration of iv high caloric soln (1,800 cal/day) (IVH), and the change in the concentration of these hormones was compared by the paired t-test. Before IVH administration the concentrations of T4, rT3 and TSH were within the normal range, but that of T3 was low in nine patients, six of whom had values below the detectable range (less than 17 ng/dl). The concentration of TBG was normal. After IVH was administered, the concentrations of T4, rT3 and TBG were significantly lowered. The concentration of T3 increased in three patients but was still not detectable in six. There was no significant change in TP concentration in the serum. Sato lung cancer was transplanted sc into the backs of male Donryu rats, and the concentrations of T3, T4 and TSH in the blood were measured at the beginning and 2-6 wk after transplantation. The concentration of T3 changed from 33.2 +-7.5 ng/dl to 24.4 +-10.2 ng/dl during the first 2 wk. However, the concentrations of T4 and TSH were not significantly changed. There was no change in the concentration of T3, T4 or TSH in the controls during the 2 wk. A negative correlation was observed between cancer wt/body wt and concentration of T3 in the blood. The affinity between T3 and hepatic nuclei (Ka) and their max binding capacity (Cmax) in tumor-bearing rats was not significantly different from those in the controls. (1 Ref) (In JPN)

23. BASAL AND PENTAGASTRIN-STIMULATED LEVELS OF CALCITONIN IN THYROID AND PERIPHERAL VEINS DURING NORMOCALCEMIA AND CHRONIC HYPERCALCEMIA IN HUMANS.

Ericsson M, Berg M, Ingemansson S, Jernby B, Jarhult J
Dept. Surgery, Univ. Lund, S-221 85 Lund, Sweden
Ann Surg; 194(2):129-133 1981

The calcitonin secretion from the thyroid C-cells was studied with a peroperative method. The calcitonin concentrations in thyroid venous effluent and peripheral veins were determined in patients who underwent operations because of thyroid and parathyroid disease. In normocalcemia the thyroid vein level of calcitonin was significantly higher than that in the peripheral vein. In chronic hypercalcemia no gradient over the thyroid was demonstrable. After injection of pentagastrin into a thyroid artery a very pronounced, but transient, increase in calcitonin concentration was registered. No difference in peak value between normo- and hypercalcemia was demonstrable. The peripheral vein level was unchanged. The peroperative method is very sensitive. A marked peak in the thyroid vein corresponds to unchanged values in the peripheral vein. The method invites further studies with other secretagogues and receptor-blocking substances. (Author abstract) (21 Refs)

24. MEDULLARY CARCINOMA OF THE THYROID (CLINICAL AND ENDOCRINOLOGICAL FEATURES OF THE THYROID).

Degli Uberti EC, Trasforini G, Bagni B, Liboni A, Pasini GC, Altavilla G
Istituto di Clinica Medica Generale e Terapia Medica, Universita degli Studi di Ferrara, 44100 Ferrara, Italy
Ric Clin Lab; 11(2):171-178 1981

The results of clinical and endocrinological examination of six women (aged 20 to 64 yr) with medullary thyroid carcinoma are reported. Basal and stimulated calcitonin (CT) plasma levels were recorded in five patients. All patients underwent total thyroidectomy with bilateral radical neck dissection. Two mo after the thyroidectomy, only two patients showed normalization of basal and stimulated plasma CT levels. These findings indicate high diagnostic and prognostic efficacy of CT assay. (15 Refs)

25. COMBINING PROVOCATIVE AGENTS OF CALCITONIN TO DETECT MEDULLARY CARCINOMA OF THE THYROID.

Sisson JC, Gross MD, Frietas JE, Jackson CE, England BG
Nuclear Medicine Div., Univ. Michigan Medical Center, Ann Arbor, MI, 48109
Henry Ford Hosp Med J; 29(2):75-80 1981

Pentagastrin injection was combined with calcium ion infusion into a single stimulus of calcitonin secretion to detect medullary carcinoma of the thyroid (MCT) in persons from nine families in which MCT was found in more than one member, and in 38 paid healthy volunteers. In general, the combined pharmaceuticals provoked serum calcitonin responses equal to or greater than those of the more potent single agent. No false positive patterns were encountered, and no false negatives were seen compared with single stimuli. Patient acceptance was good. (14 Refs)

26. PLASMA CALCITONIN AS A MARKER OF DISEASE ACTIVITY IN PATIENTS WITH SMALL CELL CARCINOMA OF THE LUNG.

Wallach SR, Royston I, Taetle R, Wohl H, Deftos LJ
(c/o Deftos) 111C, Veterans Admin. Medical Center, 3350 La Jolla Village Drive, San Diego, CA, 92161
J Clin Endocrinol Metab; 53(3):602-606 1981

To evaluate the usefulness of plasma calcitonin as an index of tumor burden and disease activity, we undertook a prospective study of serial calcitonin measurements in a group of patients with small cell carcinoma of the lung from diagnosis throughout a period of intensive therapy. Plasma calcitonin was significantly elevated in 84% of patients with extensive small cell carcinoma of the lung and was not elevated in patients with limited disease at the time of diagnosis. The elevated values fell significantly in response to chemotherapy and radiation therapy, and reflected regression of followable disease and improvement in clinical status. A significant correlation existed between plasma calcitonin and extent of disease. Relapse was generally associated with an increase in elevated plasma calcitonin levels, and calcitonin appeared to reflect tumor burden. The serial measurement of plasma calcitonin is useful in the management of the patient with small cell carcinoma of the lung. (Author abstract) (16 Refs)

27. IMMUNOREACTIVE PARATHYROID HORMONE IN THE SERUM IN MYELOMATOSIS. A DESCRIPTIVE CLINICAL INVESTIGATION.

Hansen OP, Christensen MS, Birgens HS, Wantzin PS
Haematologisk afsnit, Kobenhavns kommunes Hvidovre hospital, Copenhagen, Denmark
Ugeskr Laeger; 143(30):1908-1911 1981

The serum immunoreactive parathyroid hormone (iPTH) levels were determined in 17 untreated patients with myelomatosis (eight men and nine women, 54-79 yr old) and correlated with other biochemical findings. Hypercalcemia was found in seven cases. There was no correlation between the serum Ca and corrected serum Ca levels, on one hand, and the renal glomerular filtration rate (GFR). The serum phosphate concentration was increased in 6/13 tested patients: negative correlation was found between the serum phosphate level and the GFR. The N-terminal iPTH level was reduced in eight patients (p less than 0.01), including in 6/7 patients with hypercalcemia. There was no significant correlation between the N-iPTH level and the corrected serum Ca level, but there was a positive correlation between the N-iPTH level and the CFR, especially in normocalcemic patients. The serum C-terminal iPTH level was increased in 10 patients, including in 5/7 patients with hypercalcemia. There was no significant correlation between the C-iPTH level and the correct Ca level, but an insignificant negative correlation was found between the serum phosphate and C-iPTH levels. The findings suggest that the biological parathyroid hormone secretion is reduced and still under dominant control of the serum Ca level in patients with myelomatosis, including those with reduced GFR and phosphate retention in the serum. (15 Refs) (In DAN)

28. ENDOCRINOPATHY ASSOCIATED WITH PINEAL TUMORS (2).

Mori K
Dept. Neurosurgery, Nagasaki Univ., Nagasaki 852, Japan
Neurol Med Chir (Tokyo); 21(5):447-455 1981

Pineal gland tumors and their relationship to pineal hormone, hamartoma, and luteinizing hormone-releasing hormone are discussed. Detection and pharmacological uses of melatonin are reviewed together with the case history of a 10-yr-old boy treated for pineal tumor. (112 Refs) (In JPN)

29. GUT HORMONES AND GUT ENDOCRINE TUMOR SYNDROMES.

Buchanan KD
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J Appl Med; 7(7):533-537,539 1981

A brief discussion concerning the field of gut endocrinology is presented together with a description of the clinical and diagnostic features of the gut endocrine tumors (GETs). GETs most commonly arise in the pancreas or small bowel and have four main patterns: cord-like, ribbon, alveolar, and an undifferentiated trabecular or medullary structure. They are further histologically classified into those containing enterochromaffin cells and those containing nonenterochromaffin cells. An islet cell origin is common for tumors of the nonenterochromaffin cells. The enterochromaffin cell type of argentaffinomas arise commonly in the small bowel but may also occur in the bronchus, islets, stomach, biliary tract, and large bowel. Any pancreatic tumor or small-bowel tumor or an atypical bronchial tumor should be suspected of being a GET. GETs occurring in an unusual site, as well as hepatic metastases of GETs, may be confused with anaplastic carcinoma. GETs are not as invasive as nonendocrine cancers and have a relatively good prognosis. The most common clinical features are hepatic metastases, diarrhea, diabetes mellitus, and signs of a pancreatic mass. The clinical features and diagnostic methods for the following GETs are discussed in detail: carcinoid syndrome, insulinomas, Zollinger-Ellison syndrome, glucagonoma syndrome, Verner-Morrison syndrome, and somatostatinomas. Radiologic methods and hormone assays may be useful in the diagnosis of GETs. Selective celiac axis angiography is particularly useful for demonstrating insulinomas, and superior mesenteric and celiac axis angiography displays most carcinoid tumors. Other diagnostic methods include transhepatic sampling with hormone assays and multiple hormone assays in different possible venous drainage sites of the tumor. A table listing the clinical indications for specific hormone assays is provided. The author believes that an increased clinical awareness of the GET syndromes plus the development of screening programs may result in an earlier and increased number of diagnoses of GETs. (20 Refs)

30. SCREENING OF TYPE A GASTRITIS.

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Second Dept. Medicine, Univ. Central Hosp., SF-00290 Helsinki 29, Finland
Ann Clin Res; 13(3):133-138 1981

The most reliable methods (without intubation) for screening for type A gastritis are the determinations of serum plasminogen group I and serum gastrin. The combination of low serum pepsinogen I level (less than 20 ng/ml) and high serum gastrin (more than 100 picomoles/liter) has the specificity and predictive value of a positive test of 100% for type A gastritis. The sensitivity and specificity of achlorhydria, low serum pepsinogen group I (PG I), high serum gastrin, low PG I together with high serum gastrin, and parietal cell antibodies for type A gastritis with or without pernicious anemia in pernicious anemia families were, respectively, 96.2% and 98.5%, 96.2% and 97.0%, 78.3% and 97.4%, 78.2% and 100%, and 46.5% and 88.2%. The predictive values of a positive and negative test, respectively, for these same parameters were, respectively, 97.4% and 98.5%, 94.9% and 97.8%, 94.2% and 89.2%, 100% and 89.9%, and 69.0% and 74.4%. (10 Refs)

31. DIMETHYLTRIAZENOIMIDAZOLE CARBOXAMIDE THERAPY OF ISLET CELL CARCINOMA OF THE PANCREAS.

Awrich AE, Peetz M, Fletcher WS
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J Surg Oncol; 17(4):321-326 1981

Four patients with metastatic glucagonoma and one patient with metastatic diarrheogenic islet cell carcinoma of the pancreas were treated with dimethyltriazenoimidazole carboxamide (DTIC), 250 mg/M2 daily for 5 days repeated every 4 wk. All patients responded clinically and chemically in one or more ways by a reduction in plasma glucagon levels, improved glucose tolerance, decreased measurable tumor, wt gain, and resolution of necrolytic migratory erythema and diarrhea. This experience and other cases from the literature call for the investigation of DTIC as the initial therapy in metastatic islet cell carcinoma of the pancreas and as being of possible benefit in other tumors of neuroendocrine origin. (Author abstract) (18 Refs)

32. PROTEAN MANIFESTATIONS OF NEONATAL HYPERINSULINISM.

Mayer T, Matlak ME, Lowry SF, Gooch WM, Johnson DG
804 Poplar Ridge Drive, Chesapeake, VA, 23320
Ann Surg; 194(2):140-145 1981

Endogenous hyperinsulinism is the leading cause of persistent hypoglycemia in children under 1 yr of age. Classically, the symptoms of neonatal hypoglycemia have been referable to CNS dysfunction, with seizures described in nearly all patients. Our experience with eight neonates emphasizes the protean manifestations of this disease. One patient presented with a maternal history of diuretic use, and developed asymptomatic hyperinsulinism documented by provocative testing. The hyperinsulinism cleared after 2 wk of medical therapy. This transient hyperinsulinism may have been secondary to use of a thiazide-type diuretic. A second patient presented, as a neonate, with a large abdominal mass but no seizure activity. Exploratory laparotomy revealed an 11 x 5 x 3 cm pancreatic tumor, which required splenectomy, 60% gastrectomy and duodenectomy for removal. Histologic examination demonstrated an insulin-secreting hamartoma. A third patient died suddenly without prior symptoms, and was found to have striking nesidioblastosis on pathologic examination. One infant presented with absence of the abdominal musculature (prune belly syndrome) and features of the Beckwith-Wiedeman syndrome, as well as profound hypoglycemia. Only three patients had seizures, and an additional patient had jitteriness. Pathologic diagnoses were nesidioblastosis (n = 2), islet cell hyperplasia (n = 1), adenoma (n = 1), hamartoma (n = 1), transient hyperinsulinism (n = 1). One patient's pancreas showed areas of nesidioblastosis, islet cell hyperplasia, and a discrete adenoma in the region of the common bile duct. Careful diagnostic testing is essential in these patients, inasmuch as hypoglycemia is poorly tolerated by neonates and infants. Using the diagnostic algorithm presented here, all patients' endogenous hyperinsulinism was documented quickly and efficiently. Recognition of the broad spectrum of symptoms with which these patients may present is essential if serious neurologic sequelae are to be avoided. (Author abstract) (15 Refs)

33. OPERATIVE PROCEDURE AND INDICATIONS FOR SURGICAL MANAGEMENT OF PULMONARY METASTASIS OF CHORIOCARCINOMA.

Imaizumi M, Suyama M, Akiyama S, Kondo T, Kaseki S, Tomoda Y
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Jpn J Surg; 11(4):256-262 1981

Records of 19 patients (24-60 yr old) who underwent surgery for pulmonary metastases from choriocarcinoma were reviewed to assess the value of surgery and the possible relationship between human chorionic gonadotropin (hCG) titer and survival. Among 17 patients in whom urinary hCG titer was determined preoperatively, 3 showed marked elevation; all died of distant metastases postoperatively. In the remaining 14 patients, the titer was less than 1,100 milliUnit/ml, and in 10 of these patients, it was less than 200 milliU/ml. Thoracotomy was performed 21x in 19 patients, wedge resection 16x in 14 patients, and lobectomy 5x in the remaining 5 patients. Active trophoblastic cells were identified in 15 patients; the pulmonary lesion proved to be hematoma in the remaining 4 patients. Eight of nine patients with pulmonary choriocarcinoma showed a cellular response (ie, temporary increase in hCG titer in response to chemotherapy) preoperatively, whereas only one of the four with pulmonary hematoma showed such a response. If the preoperative hCG titer is low and a cellular response is present, surgical intervention should be considered. Since regional lymph node metastasis was not evident in any patient, extensive pulmonary surgery appears to be unnecessary. (9 Refs)

34. IMPROVED HUMAN CHORIONIC GONADOTROPIN DETECTION WITH CARBOXYL-TERMINAL RADIOIMMUNOASSAY OF THE BETA SUBUNIT ON CONCENTRATED 24-HOUR URINE IN PATIENTS WITH TESTICULAR CANCER.

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Surgery Branch, NCI, NIH, Bethesda, MD, 21205
J Urol; 126(2):176-178 1981

The value of measuring serum levels of human chorionic gonadotropin in detecting and monitoring testicular cancer has been demonstrated convincingly. In this study the human chorionic gonadotropin was extracted by the kaolin-acetone procedure from 24-hr urine specimens and the total vol of the extract was adjusted to 15 ml. With a highly specific immunoassay system (H93) that recognizes the unique carboxyl-terminal peptide of human chorionic gonadotropin beta subunit (residue numbers 123 to 145) as described previously, the urinary human chorionic gonadotropin was measured serially in 32 specimens of 15 patients with initially human chorionic gonadotropin-producing testicular tumors. These 15 patients had simultaneous measurements of serum human chorionic gonadotropin using an antiserum against the beta subunit (Sb6) and urinary human chorionic gonadotropin concentrates using H93 radioimmunoassay. The initial serum hormone levels of these 15 patients were elevated and returned to normal after therapy. However, despite this occurrence the urinary hormone levels also were elevated. The initial five patients with elevated urinary but normal serum human chorionic gonadotropin levels had recurrence. The use of this highly specific radioimmunoassay in measuring urinary human chorionic gonadotropin coupled with effective chemotherapeutic agents has been valuable in selecting patients in whom further therapy is warranted despite normal serum human chorionic gonadotropin and clinically undetectable tumor. (Author abstract) (9 Refs)

35. CLONIDINE-SUPPRESSION TEST. A USEFUL AID IN THE DIAGNOSIS OF PHEOCHROMOCYTOMA.

Bravo EL, Tarazi RC, Fouad FM, Vidt DG, Gifford RW

Res. Div., Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH, 44106

N Engl J Med; 305(11):623-626 1981

A safe and simple test for pheochromocytoma (PCC) was developed involving the ability of clonidine (CLO) to suppress plasma norepinephrine levels in normal human beings by stimulating central alpha-adrenergic receptors. Ten patients with surgically proven PCC and 15 patients suspected of having PCC because of clinical symptoms, but considered free of PCC on the basis of further studies, were tested for their reaction to CLO. In the 10 patients with PCC, a single po dose of 0.3 mg CLO had no effect on plasma norepinephrine after 180 min. In the 15 patients who were hypertensive but had no PCC, plasma norepinephrine was suppressed after taking CLO. CLO had no effect on elevations of plasma epinephrine in PCC patients, while it caused an appropriate decrease in the one patient without PCC who had initial high levels. Both groups had similar basal blood pressures and heart rates. This test is considered an adjunctive test to be used particularly when hypertensive patients with 'spells' suggestive of PCC are found to have biochemical evidence of excessive catecholamine production. (13 Refs)

36. ROLE OF BIOGENIC AMINES AND THEIR RELATED ENZYMES IN CANCER CASES.

Prasad GC, Chaurasiya J, Mohanty S

Inst. Medical Sciences, Banaras Hindu Univ., Varanasi 5, India

Indian J Cancer; 18(2):103-107 1981

Serotonin, gamma-aminobutyric acid (GABA), glutamate, monoamine oxidase (MAO), and histaminase (HIS) were estimated in the plasma of 24 cancer patients and were compared to values from 36 patients with brain tumors. There were 10 patients with breast cancer, 5 with stomach cancer, 3 with thyroid cancer, 3 males with hypernephroma, and 1 male each with leukemia, lymphosarcoma, and seminoma of the testes. Serotonin was significantly higher in most of the patients compared with normal controls, with max increases in cases of breast cancer, stomach cancer, and myeloid leukemia. Significant decreases in MAO values were noted in most of the cancer patients. Brain tumors demonstrated a significant increase in MAO levels. Plasma HIS was elevated in all cancer cases, with the most significant increase in the case of seminoma of the testes. GABA was below normal levels in all cancer cases except those of the brain, stomach or seminoma testes. Glutamate was significantly increased in cancer patients compared with normal controls. The use of these biogenic amines and their related enzymes for the diagnosis and progress and therapeutic decisions of cancer management is suggested. (20 Refs)

37. SEROTONIN AND HISTAMINE METABOLISM IN THE LUNGS IN VARIOUS SURGICAL PATHOLOGIES, AND THE EFFECT OF ITS CHANGES ON THE PULMONARY CIRCULATION AND INTRAOPERATIVE INTRAPULMONARY SHUNTING.

Gimmel'farb GN, Islambekov ES, Gerasimov NM, Nazyrova LA, Kleinerman VE, Nigmatullaeva MKh
Branch of All-Union Res. Inst. Clinical and Experimental Surgery, Tashkent, USSR
Grudn Khir; (4):76-79 1981

Metabolism of serotonin (ST) and histamine (HA) in the lungs was studied in 43 surgical patients (29 men, 43 women; 13-54 yr old). There were 20 patients with pulmonary echinococcosis, 13 with chronic lung diseases, and 10 with lung neoplasms. Preoperatively, the patients with lung neoplasms had the highest blood levels of endogenous ST and HA. Intraoperative factors did not affect HA metabolism but reduced the ST release into the arterial blood. (22 Refs) (In RUS)

EFFECTS ON NORMAL AND NEOPLASTIC CELLS AND TISSUES

38. GROWTH HORMONE STIMULATION OF NORMAL AND LEUKEMIC HUMAN T-LYMPHOCYTE PROLIFERATION IN VITRO.

Mercola KE, Cline MJ, Golde DW
Div. Hematology-Oncology, Dept. Medicine, Univ. California Los Angeles Center for Health Sciences, Los Angeles, CA, 90024
Blood; 58(2):337-340 1981

In order to investigate the effect of human growth hormone on T lymphocytes, we utilized a clonogenic assay for mitogen-responsive human peripheral blood T lymphocytes. Lymphocytes were purified by density gradient centrifugation and incubated in the presence of phytohemagglutinin using a two-layer agar technique for CFU-T-lymphocyte culture. Nanog concentrations of human growth hormone, ovine prolactin, human chorionic somatomammotropin, or growth hormone fragment were added to cell cultures. Growth hormone potentiated normal T-cell colony formation in a species-specific manner. Cells from a homogeneous T-lymphoblast line derived from a patient with a T-cell variant of hairy cell leukemia also showed augmentation of colony growth in the presence of human growth hormone. These studies provide evidence for a direct effect of growth hormone on normal and some neoplastic human T cells. (Author abstract) (33 Refs)

39. INHIBITION OF CLONOGENIC GROWTH OF MELANOMA CELLS BY COMBINATION OF MELANOCYTE STIMULATING HORMONE AND THEOPHYLLINE.

Wick MM
Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
J invest Dermatol; 77(3):253-255 1981

The combination of MSH and theophylline is synergistic in inhibiting the growth as well as stimulating the differentiation of pigmented melanoma cells. In order to determine if a permanent alteration in the proliferative potential of these cells was achieved, we examined the effect of MSH and theophylline alone and in combination upon the plating efficiency and tumorigenicity of S-91 Cloudman melanoma cells. Following treatment with the combination of MSH and theophylline, the cells became deeply pigmented and had their colony forming ability reduced to 28% of control. Neither MSH or theophylline alone, although effective in reducing the growth rate of the cells, caused a significant reduction in clonogenic growth. When cells were pretreated with MSH and theophylline alone or in combination and reinjected into mice, the combination of MSH and theophylline caused a significant reduction in percentage of animals developing tumor (reduced to 14% of control). Cells treated with either MSH or theophylline alone were similar in their tumorigenic potential to control cells. These effects were selective since the nonmelanocytic control cells, mouse fibroblast L929 and Chinese hamster ovary when treated similarly did not exhibit any alteration in their clonogenic potential. The treatment of responsive cells with the combination of MSH and theophylline is capable of causing permanent decrease in the proliferative potential of murine melanoma cells and may have relevance to the treatment of this disease in man. (Author abstract) (12 Refs)

40. FAILURE OF SOMATOSTATIN TO INFLUENCE EXPERIMENTAL TUMOR CELL GROWTH IN VIVO AND IN VITRO.

Lenzhofer R, Cerni C, Frohlich I, Prager J, Pointner H
1st Dept. Medicine, Lazarettgasse 14, A-1097 Vienna, Austria
Experientia; 37(9):1015-1017 1981

The influence of somatostatin on tumor cell growth was studied in vivo in mice (sarcoma 180 ascites tumor and Lewis lung tumor) and in vitro on nontransformed and polyoma-transformed cell lines. Four or 20 ug/100 g of cyclic somatostatin and 4 ug/100 g of linear protamine Zn-bound somatostatin were injected sc twice daily in the in vivo study. Cyclic somatostatin (1, 4 or 10 ug/ml) was added twice daily to the cell cultures. Somatostatin administration influenced neither the survival of animals nor the growth rate of cultured cell lines. (Author abstract) (9 Refs)

EFFECTS OF ENDOGENOUS AND EXOGENOUS AGENTS ON NON-STEROID HORMONE ACTIVITY

41. ACTH SECRETION FROM PITUITARY ADENOMAS OF CUSHING'S DISEASE IN VITRO.

Nakane T, Kuwayama A, Okada C, Watanabe M, Yoshida J, Kageyama N
Dept. Neurosurgery, Nagoya Univ. Sch. Medicine, Nagoya, Japan
Nippon Naibunpi Gakkai Zasshi; 57(3):270-281 1981

The autonomy of ACTH secretion in Cushing's disease was studied. Adenoma tissue explants from eight patients were placed in primary culture immediately after surgical removal. These explants secreted high levels of ACTH for as long as 1 mo. ACTH secretion by residual anterior pituitary tissue in Cushing's disease patients, as well as normal pituitary tissue showed a decrease to undetectable levels within 1 mo. Adenoma tissue was perfused with lysine-vasopressin. In seven of eight cases, ACTH secretion was induced. Little or no latency period was noted. No dose-response relationship was detected. Dexamethasone inhibited ACTH secretion in only one of four cases. Experimental results agree with clinical findings that selective adenectomy produces clinical improvement and a return to normal pituitary function, including normal diurnal rhythm. Autonomy of ACTH secretion apparently is derived from adenoma tissue in Cushing's disease. The primary lesion is evidently in the pituitary gland, rather than the hypothalamus. (39 Refs) (In JPN)

42. HORMONAL INDUCTION OF KIDNEY TUMOURS IN MALE HAMSTERS. INHIBITION OF GROWTH BY A PHENOTHIAZINE DERIVATIVE (PERPHENAZINE).

Saluja PG, Hamilton JM, Thody AJ
Dept. Anatomy, Sch. Medicine, Aberdeen, Scotland
Eur J Cancer Clin Oncol; 17(7):767-773 1981

Experiments have shown that long-term treatment of male hamsters with estrogen will cause renal carcinomas, neoplastic changes in the pars intermedia of the pituitary and highly elevated levels of melanocyte-stimulating hormone (MSH). To test if MSH was fundamentally involved in renal carcinogenesis, a group of hamsters was treated for 317 days with perphenazine which is known to elevate MSH levels. A second group was treated with estrogen while a third received a combination of estrogen and perphenazine for a similar period of time. Serum MSH levels were significantly elevated in the perphenazine group but kidney tumors were absent. All estrogen-treated animals developed kidney tumors but only 19% of those given the combined treatment developed kidney tumors despite highly elevated levels of MSH. The findings suggest that MSH does not play a significant role in renal carcinogenesis in the hamster. Perphenazine may inhibit the induction of estrogen-induced tumors by competing with estrogen for receptors in the kidney or may protect cells from toxic injury by stabilizing cell and microsomal membranes. The phenothiazines are known to induce, and increase the activity of, microsomal enzymes and that may lead to enhanced detoxification of the carcinogen. Other effects of phenothiazines include elevation of prolactin levels. The fact that the body wt of animals treated with DES and perphenazine was significantly lower than that of the other groups may indicate that the reduction in tumor incidence was the result of a certain degree of undernutrition. Further work is required to elucidate the mechanism of tumor inhibition by phenothiazine derivatives. (Author abstract) (32 Refs)

43. THE EFFECT OF PHENFORMIN, L-DOPA AND PARACHLOROPHENYLALANINE TREATMENT OF IMMUNE RESPONSE AND CHEMICAL CARCINOGENESIS DEVELOPMENT IN BALB/C MICE.

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R. E. Kavetsky Inst. Oncology of Acad. Science of Ukrainian SSR, Kiev, USSR
Vopr Onkol; 27(6):45-50 1981

Treatment with 20-methylcholanthrene resulted in the increase in hypothalamic levels of noradrenaline and serotonin in BALB/c mice. Immunization of carcinogen-treated animals with ovine RBCs was followed by changes in the hypothalamic levels of central neurotransmitters, opposite to those in intact immunized controls. After correction of the levels of neurotransmitters in the hypothalamus with phenformin, parachlorophenylalanine or L-dopa carried out prior to immunization, the fraction of antibody-producing cells in the spleen of carcinogen-treated mice returned to normal. A combined administration of immunostimulators and drugs for correction of hypothalamic levels of noradrenaline and serotonin potentiated inhibitory effect of the former on chemical carcinogenesis. (Author abstract) (15 Refs) (In RUS)

44. INSULIN AND GLUCAGON IN RATS WITH ISLET CELL TUMORS INDUCED BY SMALL DOSES OF STREPTOZOTOCIN.

Yoshino G, Kazumi T, Morita S, Baba S
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Can J Physiol Pharmacol; 59(8):818-823 1981

Plasma insulin and glucagon responses to oral glucose loading were examined in rats with islet cell tumors induced by a single iv injection of streptozotocin (30 or 40 mg/kg body wt). Twenty-four macroscopic and six microscopic tumors occurred in 21 rats. In 15 of 21 tumor-bearing rats, there was exaggerated insulin release in response to oral glucose. Plasma glucose levels did not rise with the oral glucose load and were comparable to those seen in normal animals. Hence these rats are described as having 'responsive tumors.' In six rats with 'nonresponsive tumors' there was no insulin response and the plasma glucose levels rose. No significant differences in plasma glucagon levels were observed between the two groups. Nonresponsive tumors as well as responsive tumors contained a significant amount of extractable insulin (17.68 +-8.60 and 35.07 +-10.05 mg/g wet wt, respectively) and detectable amounts of immunoreactive glucagon (1.47 +-0.61 and 2.24 +-0.67 ug/g wet wt, respectively). These results suggest that a small dose of streptozotocin produces two types of islet cell tumors. One is insulin producing and insulin secreting whereas the other is insulin producing but not insulin secreting. (Author abstract) (14 Refs)

45. SYNTHESIS OF IMMUNOREACTIVE INSULIN IN VITRO BY APLASTIC MAMMARY CARCINOMA PRECO NDITIONED IN DIABETIC MICE.

Pavelic K, Ferle-Vidovic A, Osmak M, Vuk-Pavlovic S
Rudjer Boskovic Inst., P.O. Box 1016, Bijenicka 54, 41001 Zagreb, Croatia, Yugoslavia
JNCI; 67(3):687-688 1981

Direct evidence is presented that the murine aplastic carcinoma, preconditioned in diabetic mice, secreted immunoreactive insulin (IRI) in vitro for at least 25 days. The intensity of in vitro IRI secretion depended on the length of the in vivo preconditioning. (Author abstract) (8 Refs)

46. SYNTHESIS OF GLYCOPROTEIN HORMONE ALPHA SUBUNIT AND PLACENTAL ALKALINE PHOSPHATASE BY HELA CELLS: EFFECT OF TUNICAMYCIN, 2-DEOXYGLUCOSE, AND SODIUM BUTYRATE.

Cox GS
Dept. Biochemistry and Biophysics, Iowa State Univ., Ames, IA, 50011
Biochemistry; 20(17):4893-4900 1981

The glycoprotein hormone alpha subunit is secreted by human cervical carcinoma cells (HeLa) as an ectopic gene product. Studies were undertaken to determine whether the tumor protein is glycosylated, as is the normal placental protein, and whether protein glycosylation is a prerequisite for secretion. About 80% of the HeLa protein was adsorbed to concanavalin A-Sepharose (Con A-Sepharose) and could be eluted with 0.2 M methyl alpha-glycoside, demonstrating its glycoprotein character. Tunicamycin (TM) at concentrations between 0.25 and 2 ug/ml and 2-deoxy-D-glucose (dGlc) at concentrations between 1 and 10 mM caused only a marginal (20-40%) reduction in extracellular alpha. Neither TM nor dGlc caused a concomitant rise in intracellular alpha as the level of extracellular hormone decreased, suggesting that the inhibitors were not specifically reducing protein secretion. The possibility that alpha secreted by HeLa cells in the presence of TM was glycosylated prior to the drug's addition and subsequently released seems unlikely in view of the kinetics of alpha secretion following TM addition. The carbohydrate content of alpha synthesized in the presence of TM was examined by immunoprecipitation of culture media from cells grown in the presence of [3H]glucosamine and 14C-labeled amino acids and by chromatography of media on Con A-Sepharose. In the presence of TM at 2 ug/ml, alpha polypeptide synthesis was decreased by about 40% while alpha glycosylation was inhibited by 92%. These results suggest that glycosylation of alpha is not required for secretion since almost total inhibition of glucosamine incorporation caused a reduction in alpha levels no greater than could be accounted for by the moderate inhibition of general protein synthesis caused by this agent. The proportion of alpha not bound to Con A-Sepharose increased when TM was present, but a fraction of the alpha secreted in the presence of TM contained at least some carbohydrate since it was still retained by the lectin. Thus, the possible contribution of a minor oligosaccharide component, resistant to TM, in the facil itation of alpha release cannot be totally excluded. Addition of sodium butyrate to cultures resulted in a 10-fold increase in alpha production and a 5-fold increase in the synthesis of placental alkaline phosphatase (PAP), a membrane-bound glycoprotien. Deoxyglucose caused a drastic reduction in the butyrate-induced synthesis of both alpha and PAP down to uninduced levels. That the glycosylation inhibitors reduced the butyrate-stimulated synthesis of alpha and alkaline phosphatase to a greater extent than their basal levels of synthesis suggests the possibility that butyrate may enhance the accumulation of these proteins by a mechanism that is particularly sensitive to these compounds. (Author abstract) (43 Refs)

47. MURINE ERYTHROPOIETIN IN ASCITIC FLUID:

Fredrickson TN, LoBue J, Camiscoli JF, Gordon AS, Spector D
Dept. Pathobiology, Univ. Connecticut, Storrs, CT, 06268
J Surg Oncol; 17(4):379-383 1981

Administration of 0.2 ml of a 1.25% soln of phenylhydrazine (PHZ) and 500 rads of x-irradiation to BALB/c mice produced a prompt and severe reduction to hematocrit with a resultant increase in plasma levels of erythropoietin (Ep). By also giving mice treated with PHZ and irradiation an ascites form of a transplantable sarcoma, the amount of recoverable material rich in Ep could be greatly increased because ascitic fluid contained levels of Ep comparable to plasma. (Author abstract) (9 Refs)

RECEPTOR/ BINDING SITES

48. THYROID HORMONE RECEPTORS IN HUMAN BREAST CANCER.

Cerbon MA, Pichon MF, Milgrom E
Groupe de Recherches sur la Biochemie Endocrinienne et la Reproduction, INSERM U. 135, Faculte de Medicine Paris-Sud, 94270 Bicetre, France
Cancer Res; 41(10):4167-4173 1981

Optimum conditions were established for preparation of nuclei from human breast cancer biopsies. Incubation of nuclei with various concentrations of of L-3,3',5-[125I]triiodothyronine showed the presence of three binding systems: a high-affinity binding system (Type I) (KD approx 1.5 nM); an intermediate-affinity saturable system (Type II) (Kd approx 0.5 um); and a nonsaturable nonspecific system. Salt at high concentrations (0.4 M-KCl) extracted only Type I triiodothyronine-binding protein, thus simplifying its study and quantification. Type I binding protein was shown to have the affinity for triiodothyronine and the hormonal specificity usually ascribed to thyroid hormone receptors. Its sedimentation coefficient was 3.6S at 0.4 M KCl. Extractable triiodothyronine receptor was measured in 58 individual biopsies of primary and metastatic breast cancer. It was present in all tumors, but its concentration was highly variable (0.20 pmol/mg DNA; range, 0.044 to 0.702). Triiodothyronine receptor concentration was not correlated with age or endocrine status of the patient or with extension or histological grading of the tumor. Moreover, there was no correlation with estradiol and progesterone receptor concentrations. (Author abstract) (38 Refs)

49. SPECIFIC TRIIODOTHYRONINE BINDING BY TUMOR CELLS AND SPLEEN CELLS IN A THYROID HORMONE DEPENDENT MOUSE TUMOR SYSTEM.

Gupta MK, Chiang T, Deodhar SD
Dept. Immunopathology, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH, 44104
Eur J Cancer Clin Oncol; 17(7):819-823 1981

We have reported thyroid hormone dependency of syngeneic mouse tumor (fibrosarcoma T241 in C57Bl/6J mice) for growth and spread. To study further the mechanisms of thyroid hormone action we assayed tumor cells and spleen cells for thyroid hormone receptors. Cells were incubated at 37 C for 1 hr with [125I]triiodothyronine with and without unlabeled T3. Competitive inhibition of [125I]T3 bound to spleen cells was demonstrated by increasing the amount of unlabeled T3 and T4. Similar competitive inhibition of binding was minimal for intact tumor cells. Saturable binding sites in nuclei were demonstrated in all these cell populations. A Scatchard analysis of nuclei fraction from these cells showed equilibrium dissociation constant (Kd) of 0.56 x 10(-9) M for normal spleen cells and tumor cells and 1.4 x 10(-9) M for tumor-bearing mice spleen cells. The estimated max binding capacity for nuclei of these cells was 26 fmol/10 x 10(6) cells for normal spleen cells, 46 fmol/10 x 10(6) cells for tumor-bearing mice spleen cells and 45 fmol/10 x 10(6) cells for tumor cells. Our results established the presence of T3 receptors in nuclei of tumor cells as well as spleen cells and suggests the direct metabolic effect of thyroid hormone as a possible mechanism for thyroid hormone dependency of this tumor. (Author abstract) (21 Refs)

50. THE HORMONAL REGULATION AND INTERACTION OF CONCANAVALIN A AND INSULIN BINDING IN R3230AC MAMMARY ADENOCARCINOMA CELLS.

Sorge LK, Hilf R
Dept. Biochemistry, Univ. Rochester Cancer Center, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642
Biochim Biophys Acta; 676(2):187-198 1981

To investigate the effects of concanavalin A on insulin binding to R3230AC mammary carcinomas, initial experiments were performed to characterize binding of concanavalin A. Concanavalin A binding was found to be specific and saturable. Equilibrium binding experiments demonstrated that addition of low concentrations of concanavalin A enhanced the binding of concanavalin A, suggestive of positively cooperative interactions. Binding of concanavalin A was responsive to hormonal alterations; tumor cells from diabetic rats showed enhanced binding of [3H]concanavalin A and insulin compared to cells from intact rats and administration of insulin to diabetic rats returned concanavalin A and insulin binding to levels seen in controls. Incubation of tumor cells with concanavalin A prior to addition of 125I-labeled insulin resulted in a reduction of insulin-binding capacity; succinyl-concanavalin A did not affect binding of insulin. The percent inhibition of insulin binding by concanavalin A was highest at the lower insulin concentrations, providing a linearized Scatchard plot that yielded a calculated Kd value comparable to the low-affinity portion of the curvilinear Scatchard plot for insulin binding. The dissociation rate of bound insulin depended on receptor occupancy. Addition of concanavalin A after insulin binding reached equilibrium resulted in increased insulin binding at higher hormone concentrations, decreased rates of dissociation of insulin and a loss of the correlation between receptor occupancy and dissociation rates. Concanavalin A alone demonstrated an insulin-like effect on glucose transport, which in these tumor cells represents a decrease in transport of 3-O-methylglucose. These results suggest that binding of both concanavalin A and insulin to cells from this hormonally responsive neoplasm is under insulin regulation and demonstrates similar characteristics to those reported for a variety of normal cells. Furthermore, the interaction between concanavalin A and the cell membranes affects the affinity of the insulin receptor for insulin and appears to decrease the observed negative cooperativity. (Author abstract) (58 Refs)

51. INTERACTION OF VASOACTIVE INTESTINAL PEPTIDE WITH A CELL LINE (HELA) DERIVED FROM HUMAN CARCINOMA OF THE CERVIX: BINDING TO SPECIFIC SITES AND STIMULATION OF ADENYLATE CYCLASE.

Prieto JC, Guerrero JM, De Miguel C, Goberna R
Dept. Biochemistry, Sch. Medicine, Sevilla, Spain
Mol Cell Biochem; 37(3):167-176 1981

The binding of vasoactive intestinal peptide (VIP) and its effect on cyclic AMP production were assessed in HeLa cells. The binding of [125I]VIP is a moderately rapid process, reversible, saturable, specific and dependent on temperature. Virtually no inactivation of the peptide is observed after 2 hr of exposure to the cells. At 15 C, the binding data obtained at steady state are compatible with the existence of two classes of binding sites: a first class with a Kd of 2.4 nM and low binding capacity (1.5 x 10(5) sites/cell) and a second class with a Kd of 100 nM and a high binding capacity (4.9 x 10(6) sites/cell). Secretin is eight times less potent than VIP in competing with 125I VIP but glucagon, insulin and somatostatin are inactive. VIP-induced stimulation of cyclic AMP production depends on time and temperature and is potentiated by a phosphodiesterase inhibitor. A concentration of VIP as low as 10(-10) M is able to stimulate adenylate cyclase. Half-max stimulation is observed at 10(-9) M and max stimulation (4x above basal levels) at 10(-8) M VIP. Secretin is an agonist of VIP but exhibits a 1,000x lower potency with respect to adenylate cyclase activation. Glucagon, insulin and somatostatin do not show any effect. The presence of high-affinity binding sites and the high sensitivity and specificity of adenylate cyclase for VIP in HeLa cells provide a good model to study the role of this peptide on cell proliferation and differentiation. (Author abstract) (38 Refs)

52. ADENYLATE CYCLASE COUPLED BETA ADRENERGIC RECEPTORS OF RAUSCHER ERYTHROLEUKEMIA CELLS.

Sytkowski AJ, Kessler CJ, D'Albis JN
Div. Hematology-Oncology, Children's Hosp. Medical Center, Boston, MA
Biochem Biophys Res Commun; 101(4):1221-1227 1981

Presence of beta-adrenergic receptor-adenylate cyclase complexes in Rauscher murine erythroleukemia cells (clone R19A) was examined. Cell exposure to the phosphodiesterase inhibitor isobutylmethylxanthine (IBMX: 3 milliM) for 15 min resulted in accumulation of 4 picomole cyclic AMP/10(6) cells. Addition of 0.1 uM (-) isoproterenol (a beta-adrenergic agonist) caused a 2.5x increase in cyclic AMP content to 10 picomole; the response was stereospecific. (-) Epinephrine at 0.1 uM increased cyclic AMP approx 2x to 7.8 picomole. Adding 0.1 uM (-) norepinephrine had no effect. Response to beta-adrenergic stimuli was dose-dependent. The activation constant for epinephrine was 8.9 x 10(-7), lower than in most systems studied. Addition of 5 x 10(-6) propranolol completely inhibited the epinephrine effect. Binding of [125I]iodohydroxybenzylpindolol (125IHYP) to the intact cells was used to measure beta-adrenergic receptor number; nonspecific binding to low affinity sites was reduced by the addition of 100 uM phentolamine, an alpha-adrenergic antagonist. Scatchard plot yielded an equilibrium dissociation constant for 125IHYP-receptor interaction of 320 picoM and a receptor density of 1,700/cell. The results document presence of a beta-adrenergic receptor-adenylate cyclase system in an erythropoietin sensitive continuous cell line. Examination of the role of beta-adrenergic stimuli in erythroid differentiation and of beta-adrenergic receptor development and interaction with adenylate cyclase are now possible. (22 Refs)

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HORMONES IN CANCER-RELATED BIOLOGY

Non-Steroid Hormones

SERIES CB24 No. 82/02

FEBRUARY, 1982

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CHARACTERIZATION OF NON-STEROID

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

HORMONES IN EXPERIMENTAL AND IN VITRO SYSTEMS

1. MULTIPLE FORMS OF GROWTH HORMONE: DETECTION IN MEDIUM FROM CULTURED PITUITARY ADENOMA EXPLANTS.

Talamantes F, Lopez J, Lewis UJ, Wilson CB
Div. Natural Sciences, Thimann Lab., Univ. California Santa Cruz, Santa Cruz, CA, 95064

Acta Endocrinol (Copenh); 98(1):8-13 1981

Three pituitary adenomas obtained from patients with acromegaly were maintained in organ explant culture for a period of 12 days in a defined culture medium. Lyophilized culture medium from each was then examined by electrophoresis to determine which forms of growth hormone were secreted by the explants. All three explants secreted principally the major form of growth hormone. One adenoma however secreted unusually large amounts of two slowly migrating forms which were in low concentration in the GH-containing granules of normal pituitaries. On the other hand the adenoma produced a much lower amount of a 20,000-dalton variant than was seen in normal pituitary glands. The other two adenomas did not secrete the relatively large amounts of the slowly migrating forms although the quantity of the 20,000-dalton form was less than the amount seen in the normal pituitary. There was no evidence of proteolytic alteration of the growth hormone during the culturing process. In companion experiments with rat pituitary glands the growth hormone did not undergo proteolytic degradation in the gland left in situ for 96 hr at 5 C. (Author abstract) (16 Refs)

2. HETEROGENEITY OF IMMUNOREACTIVE CALCITONIN IN EXTRACTS OF NORMAL HUMAN THYROID.

Woloszczuk W, Kovarik J
Ludwig Boltzmann-Institut fur Klinische Endokrinologie, Garnisong. 13, A-1090 Vienna, Austria

Horm Metab Res; 13(8):460-463 1981

Immunoreactive calcitonin in serum of patients with medullary carcinoma of the thyroid and in extracts of this tumor has been found to exhibit heterogeneity when analyzed by gel-chromatography and radioimmunoassay. In this study normal human thyroid tissue was homogenized in buffered saline at neutral pH and a soluble fraction was obtained after ultracentrifugation. Extracts were analyzed by gel-filtration before and after treatment with detergents, with denaturing agents and after reduction and alkylation. The stability in vitro of the extracted immunoreactive calcitonin was determined at different temperatures and the changes in heterogeneity analyzed by gel-filtration. The results suggest that at least part of the largest form of immunoreactive calcitonin is an artefact of the chromatographic procedure. Moieties with a mol wt below 12,000 Daltons were present and could be identical with prehormones described by others. However, no indication for a sequential degradation releasing calcitonin monomer from larger precursors was found in normal thyroid. (Author abstract) (14 Refs)

CLINICAL, DIAGNOSTIC AND PROGNOSTIC STUDIES

3. ANTERIOR PITUITARY HORMONE LEVELS IN THE CEREBROSPINAL FLUID OF PATIENTS WITH PITUITARY AND PARASELLAR TUMORS.

Braunstein GD, Hassen G, Kamdar V, Nelson JC
Cedars-Sinai Medical Center, Room 516, Schuman Building, 8700 Beverly Blvd., Los Angeles, CA, 90048

Fertil Steril; 36(2):164-172 1981

Cerebrospinal fluid (CSF) concentrations of growth hormone, prolactin (PRL), adrenocorticotropin, thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, and the glycoprotein hormone alpha subunit were determined in 30 patients with pituitary and parasellar tumors. Although many of the patients had elevated hormone levels, no differentiation between patients with intrasellar tumors and those with pituitary tumors with suprasellar extension or primary suprasellar tumors could be made based upon the absolute CSF hormone concentration. A highly significant correlation between serum and CSF PRL concentrations was found (r = 0.87; P less than 0.001), suggesting that CSF PRL is derived from the serum. No correlation was found between the serum and CSF concentrations of the other anterior pituitary hormones. (Author abstract) (25 Refs)

4. PROLACTIN SECRETION IN CUSHING'S DISEASE.

Caufriez A, Desir D, Szyper M, Robyn C, Copinschi G
Human Reproduction Res. Unit, Dept. Obstetrics and Gynecology, Hopital Saint-Pierre, Rue Haute 322, B-1000 Brussels, Belgium

J Clin Endocrinol Metab; 53(4):843-846 1981

PRL secretion was evaluated in 11 patients with Cushing's disease (7 women, 4 men). Basal morning levels were elevated when compared to normal subjects. PRL reactivity to TRH and hypoglycemia was normal in most patients. The 24-hr mean PRL levels were elevated, with partial or total alteration of the nyctohemeral rhythm. Cure of Cushing's disease by selective pituitary adenomectomy restored a normal PRL secretion. (Author abstract) (13 Refs)

5. PLASMA CONCENTRATIONS OF C-19 STEROIDS, ESTROGENS, FSH, LH AND PROLACTIN IN POST-MENOPAUSAL WOMEN WITH AND WITHOUT BREAST CANCER.

Bird CE, Cook S, Owen S, Sterns EE, Clark AF
Dept. Medicine, Etherington Hall, Queen's Univ., Stuart St., Kingston, Ontario K7L 2V7, Canada

Oncology; 38(6):365-368 1981

The plasma levels of 5alpha-dihydrotestosterone, testosterone, delta5-androstene-3beta,17beta-diol, delta4-androstenedione, dehydroepiandrosterone, estrone, estradiol, dehydroepiandrosterone sulfate, follicle stimulating hormone, luteinizing hormone and prolactin were measured in normal post-menopausal women and in post-menopausal women with proven breast cancer. The mean prolactin level was significantly higher (p less than 0.01) and the mean 5alpha-dihydrotestosterone level lower (p less than 0.05) for the women with breast cancer. There were no significant differences for any of the other hormones. As well, there were no significant differences for the extent of binding of testosterone and delta5-androstene-3beta,17beta-diol to plasma proteins between the two groups of subjects. (Author abstract) (29 Refs)

6. EFFECTS OF HIGH-DOSE METHOTREXATE AND VINCRISTINE ON OVARIAN AND TESTICULAR FUNCTIONS IN PATIENTS UNDERGOING POSTOPERATIVE ADJUVANT TREATMENT OF OSTEOSARCOMA.

Shamberger RC, Rosenberg SA, Seipp CA, Sherins RJ
(c/o Sherins) Developmental Endocrinology Branch, Natl. Inst. Child
Health and Human Development, NIH, Bldg. 10, Rm B09, Bethesda, MD, 20205
Cancer Treat Rep; 65(9):739-746 1981

We have studied gonadal function in five patients (3 men and 2 women) who received high-dose methotrexate (HD-MTX) alone and in 12 patients (7 men and 5 women) who received HD-MTX and vincristine (VCR) as postoperative adjuvant therapy for osteosarcoma. Testicular function was assessed by determination of testicular size, sperm concentration, and serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone levels while evaluation of ovarian function was based on menstrual history and serum FSH, LH, estradiol, and progesterone levels. The two women who received HD-MTX and all five women who received HD-MTX and VCR had regular cyclic menses not only after therapy but also during treatment. Serum FSH, LH, estradiol, and progesterone levels were normal in all women studied. Among the 10 men studied, testicular function was normal in the 6 patients evaluated initially several mo after the completion of therapy. In contrast, severe oligospermia was noted among four men evaluated during and immediately after treatment. From serum samples obtained before, during, and after treatment we have determined that approx one half of the men who received HD-MTX alone or in combination with VCR develop transient testicular failure associated with a significant increase in serum FSH but not LH levels. Sperm concentration and serum FSH levels then return to normal after completion of chemotherapy. (Author abstract) (46 Refs)

7. BROMOCRIPTINE THERAPY IN ACROMEGALY: USE IN PATIENTS RESISTANT TO CONVENTIONAL THERAPY AND EFFECT ON SERUM LEVELS OF SOMATOMEDIN C.

Moses AC, Molitch ME, Sawin CT, Jackson IM, Biller BJ, Furlanetto R, Reichlin S
(c/o Molitch) Div. Endocrinology, Tufts-New England Medical Center, Box 268, 171 Harrison Ave., Boston, MA, 02111
J Clin Endocrinol Metab; 53(4):752-758 1981

Seven patients with clinically active acromegaly who had not responded completely to previous surgical or radiation therapy were treated with bromocriptine. Bromocriptine was well tolerated; only one of the seven patients discontinued treatment seconday to side effects. Six of the seven patients improved during bromocriptine therapy, although GH levels were normalized in only two patients. All patients had elevated levels of somatomedin C (Sm-C) before therapy even when basal levels of GH were less than 10 ng/ml. One patient normalized both GH and Sm-C during bromocriptine therapy and had an excellent clinical response. Five patients had moderately good clinical responses; four of these patients had substantial falls in GH levels, but Sm-C levels fell minimally if at all in four and actually increased in one patient. In one patient, there was no change in clinical status, GH levels, or SM-C levels. Thus, the clinical response did not correlate well with changes in Sm-C in most patients. The patterns of response to provocative stimuli of GH secretion in acromegaly were maintained during bromocriptine therapy, as has been previously reported. Based on our experience, bromocriptine appears to be a useful adjunct in the therapy of acromegaly, even in patients who have had prior ablative therapy. (Author abstract) (29 Refs)

8. THYROTROPIC ACTIVITY OF THE PITUITARY GLAND AND BLOOD LEVELS OF TRIIODOTHYRONINE AND THYROXINE IN THE PATIENTS WITH UTERINE MYOMA.

Trubnikova LI
Dept. Obstetrics and Gynecology, Tadzhik Medical Inst., Dushanbe, USSR
Akush Ginekol (Mosk); (7):12-15 1981

Functional activity of the pituitary and thyroid glands was evaluated in 27 women (aged 22 to 42 yr) with uterine myomas. Determination of the blood levels of thyrotropin (TTH), thyroxine (T4), and triiodothyronine (T3) showed significant increase of TTH and estradiol with simultaneous decrease of T3 and T4 levels in the patients with ovulatory menstrual cycle. It was suggested that relationship between TTH, T3 and T4 in majority of the patients with uterine myoma reflected a primary insufficiency of the thyroid. (8 Refs) (In RUS)

9. DISAPPEARANCE OF 131I UPTAKE FROM 'HOT' THYROID NODULES FOLLOWING TSH STIMULATION.

Fanfani G, Pasculli D, Melel M, D'Addabbo A
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Radiol Med (Torino); 67(10):763-766 1981

Homeostasis and autoregulation mechanisms were studied in interglandular, functional relationships of 'hot' thyroid nodules, which after thyroid stimulation hormone (TSH) was given, stimulation become scintigraphically 'cold'. Of 73 patients with hyperfunctioning adenomas, only 25 showed decrease or disappearance of 131I from 'hot' nodule after TSH stimulation. This change was very pronounced in 8, evident in 6, and appreciable in 11. Different hypotheses, morphological and functional characteristics were discussed. These type of hyperfunctioning adenomas do not have autonomy due to their sensitivity to TSH, and exhibit peculiar histologic and ultrastructural characteristics. (12 Refs) (In ITA)

10. THYROTROPIN-RELEASING HORMONE, CHLORPROMAZINE AND L-DOPA OR BROMOCRIPTINE TESTS IN CUSHING'S SYNDROME DUE TO ADRENAL HYPERPLASIA AND ADRENAL ADENOMA.

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Dept. Internal Medicine, Natl. Taiwan Univ. Hosp., Taipei, Republic of China
J Formosan Med Assoc; 80(1):7-18 1981

Thyrotropin-releasing hormone (TRH), chlorpromazine (CPZ), and L-dopa or bromocriptine (CB 154) tests were performed in nine female patients with Cushing's syndrome, four with adrenal hyperplasia (AH) and five with adrenocortical adenomas (AA), before and after bilateral total adrenalectomy for AH and unilateral total adrenalectomy for AA to clarify the pathogenesis of Cushing's disease. In the AA patients, thyroid stimulating hormone (TSH) and prolactin (PRL) levels were similar to those of controls prior to surgery. However, the response of TSH to TRH was markedly suppressed throughout the test period. The response of PRL to TRH was quite similar to that of controls. The basal PRL levels and PRL levels after CPZ stimulation at each point showed no increase unlike controls. Similar basal serum PRL levels were observed in L-dopa suppression test, although a gradual decrease in PRL was noted. Following surgery, the basal TSH levels rose and significant response to TRH was observed. The basal serum PRL levels decreased and the PRL response to TRH was less marked. Gradual increase of PRL following CPZ stimulation was obtained. The CB154 test was the same before and after surgery. In the four AH patients, prior to surgery, the basal serum TSH level was lower than in the control and adenoma groups prior to surgery. The TSH response to TRH was significantly lower than in the control but similar to the adenoma group. Serum PRL levels were significantly decreased before and after TRH stimulation compared with those of control and adenoma groups. Unlike the adenoma group, serum PRL responded to CPZ only slightly and remained almost unchanged after L-dopa. After surgery, no change in TSH levels was observed, although a slight response to TRH was observed. A slightly greater PRL response to CPZ was noted following surgery. CB154 tests were normal before surgery but significantly elevated PRL levels with gradual suppression were obtained afterwards. The results indicated that the pathogenesis of Cushing's disease is in the pituitary. (38 Refs)

11. CUSHING'S SYNDROME: GENERAL AND SPECIAL DIAGNOSTICS.

Tenschert W, Vetter W, Fischer M, Siebenschein R, Studer A, Holland-Cunz B, Siegenthaler-Zuber G, Vetter H

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Dtsch Med Wochenschr; 106(38):1213-1216 1981

Over a 5-yr period 37 patients (28 women, 9 men) with Cushing's disease were studied. Hypophyseal-hypothalamic disregulation was present in 24 (mean age 33.8 yr), adrenal adenoma in 8 (mean age 37.1 yr), and adrenal carcinoma in 4 (mean age 54.8 yr). One patient (aged 29 yr) had Cushing's syndrome due to an ectopic ACTH overproduction in Zollinger-Ellison syndrome. Arterial hypertension was present in 31 patients. Under basal conditions the urinary excretion rate of free cortisol was evaluated in all but one of 127 specimens from the 37 patients. Levels of 17-hydroxysteroids (17-OH-CS) were above normal in only 59% (77 specimens from the 37 patients). Suppression tests with 2 mg and (or) 8 mg dexamethasone indicated marked inhibition of cortisol excretion (on measuring both free cortisol and 17-OH-CS) only in the patients with hypophyseal-hypothalamic disregulation. Plasma ACTH Values, measured in 7 of the 24 patients with central Cushing's syndrome, had a mean value of 810 pg/ml (normal up to 60 pg/ml). A Nelson syndrome developed after bilateral adrenalectomy in four patients with central Cushing's syndrome. 131I-cholesterol scan in 13 patients revealed marked bilateral increase in uptake of radioactivity in the adrenal region of five patients with hypophyseal-hypothalamic disregulation, while unilateral increased uptake was observed in the four patients with adrenal adenoma. There was no or only little activity increase in the four patients with adrenal carcinoma. The results indicate that hypercorticism can be more reliably diagnosed by measuring urinary excretion of free cortisol rather than of 17-OH-CS. The dexamethasone inhibition test (with 2 and/or 8 mg dexamethasone) indicates definite suppression of hormone excretion rates in central Cushing's syndrome. The 131I-cholesterol scan is of limited value in the diagnosis of adrenal carcinoma. (Author abstract) (no Refs) (In GER)

12. ELECTROLYTE AND METABOLIC DISORDERS IN HORMONE-PRODUCING BRONCHIAL CARCINOMA.

Hollander E, Toth Cs

III. Belgyogyaszati Osztaly, Koranyi Frigyes es Sandor Korhaz, Budapest, Hungary

Orv Hetil; 122(30):1951-1953 1981

Ectopic ACTH production was observed in three men with bronchial carcinoma. The endocrinopathy was revealed by hypokalemia and metabolic alkalosis in all cases. Symptoms of Cushing's syndrome were found in one patient only. The electrolyte and acid-base disorders damaged the skeletal, smooth and striated muscles. The clinical symptoms of ectopic ACTH production appeared before the manifestation of the carcinoma in two patients, and simultaneously with the diagnosis of the carcinoma in the third. The electrolyte and metabolic disorders aggravated the respiratory insufficiency and had an adverse effect on the course of the disease. (27 Refs) (In HUN)

13. STRESS AND NEUROENDOCRINE SYSTEM IN CANCER PATIENTS.

Rylov VV, Sviridova SP, Guliaev GV

All-Union Cancer Res. Center, Moscow, USSR

Vestn Akad Med Nauk SSSR; (8):80-83 1981

The effect of surgery and anesthesia on the pituitary-adrenal system was studied in 54 patients with cancer of the stomach, 40 with lung cancer and 105 with breast cancer. The intraoperative changes in the level of corticotropin, somatotropin, and cortisol, as well as in the degree of glycemia depended upon the type of anesthesia. The increase in the levels of corticotropin and cortisol was correlated with the severity of postoperative complications. (3 Refs) (In RUS)

14. SOME ASPECTS OF PITUITARY FUNCTION AFTER NEUROADENOLYSIS IN PATIENTS WITH METASTATIC CANCER.

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Tumori; 67(4):355-359 1981

The effects of neuroadenolysis on plasma titers of beta-endorphin, beta-lipotropin, ACTH, TSH and prolactin have been investigated in five patients with metastatic cancer who responded to the treatment and have been in remission for more than 4 yr and in five others who were undergoing the treatment for the first time for pain due to cancer metastases. Beta-endorphin, beta-lipotropin and ACTH titers were within the normal ranges of values in both categories of patients but post-neuroadenolysis titers of these peptides were higher than those before the treatment. The ability to secrete TSH and prolactin and to respond to thyroid stimulating hormone releasing hormone (TRH) remains intact following the treatment. However, whereas basal TSH titers and response to TRH was lower in the majority of patients, no such effect was observed on prolactin secretion. Plasma titers of prolactin and TSH were below the sensitivity of the method in the five patients who are in remission for more than 4 yr. These preliminary findings suggest that neuroadenolysis probably affects some mechanism(s) associated with the control of beta-endorphin, beta-lipotropin and ACTH synthesis. (Author abstract) (18 Refs)

15. RESEARCH ON SERUM MELATONIN: AGE-DEPENDENT CHANGES IN SERUM MELATONIN CONCENTRATIONS IN HEALTHY HUMAN SUBJECTS AND IN PATIENTS WITH ENDOCRINE AND HEPATIC DISORDERS AND RENAL FAILURE.

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Third Dept. Internal Medicine, Kyushu Univ. Faculty Medicine, Fukuoka 812, Japan
Fukuoka Igaku Zasshi; 72(7):423-430 1981

Changes in serum melatonin concentrations were measured with a radioimmunoassay method in 81 healthy subjects (44 men, 37 women; 1-92 yr old) and in 98 patients (15-61 yr old) with endocrine disorders, hepatic diseases, and renal failure. The patients included four with non-functioning pituitary adenomas, four with pinealomas, four with Cushing's syndrome, and two with pheochromocytomas. The mean daytime serum level of melatonin in the healthy subjects was 5.5 +-0.4 picog(pg)/ml, and the daytime serum levels decreased with advancing age. Nocturnal elevation of serum melatonin levels was diminished in the aged group of healthy subjects as compared to the younger subjects. Compared to the healthy subjects, the patients with pituitary disorders, pinealomas, thyroid dysfunction, adrenal diseases, and chronic renal failure showed no significant fluctuations in daytime serum levels of melatonin, but daytime serum levels of melatonin were elevated in patients with liver cirrhosis and acute hepatitis. (29 Refs) (In JPN)

16. SIGNIFICANCE OF SERUM CONCENTRATIONS OF CARCINOEMBRYONIC ANTIGEN, FERRITIN, AND CALCITONIN IN BREAST CANCER.

Bezwoda W, Derman D, Bothwell T, MacPhil P, Levin J, De Moor N
Dept. Medicine, Medical Sch., Hospital St., Johannesburg, S. Africa
Cancer; 48(7):1623-1628 1981

Serum concentrations of carcinoembryonic antigen (CEA), ferritin, and calcitonin were measured in 107 patients with breast cancer, 80 of whom had overt or occult metastatic disease. CEA and ferritin values were statistically higher in those patients with metastases. In contrast, there was no correlation between calcitonin concentrations and the stage of the disease. All 27 subjects with CEA concentrations greater than 80 ug/liter and 32 of 40 with values between 41-80 ug/liter had metastatic disease. Ferritin was a definite but less sensitive discriminator, with metastatic disease present in all nine patients having concentrations greater than 400 ug/liter. Such metastases were invariably hepatic. When the two measurements were used as a combined discriminant, the diagnostic accuracy increased somewhat. All 32 patients with a CEA concentration greater than ug/liter and/or a ferritin concentration greater than 400 ug/liter had metastatic disease; the same was true for 32 of the 42 subjects with CEA concentration between 41-80 ug/liter and/or a ferritin concentration between 200-400 ug/liter. The measurements and prognostic value, both when assessed alone and together, with a median survival from the time of study significantly shorter in those with the highest values. (Author abstract) (23 Refs)

17. THERAPEUTIC POSSIBILITIES IN PARANEOPLASTIC HYPERCALCEMIA.

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Med Welt; 32(32/33):1219-1221 1981

Hypercalcemia syndrome is a frequent complication in malignant diseases, occurring in 42% of mammary carcinomas, 12% of bronchial carcinomas, and 20% of plasmocytomas. Four pathophysiological causes are: (1) decalcification of bone by metastases, (2) osteoclast activating factor, (3) production of an atypical parathormone by a tumor, and (4) synthesis of atypical prostaglandin E metabolites, which mimic parathormone. Symptoms include dehydration, polydipsia, polyuria, kidney failure, vomiting, constipation, coma, and death. Therapeutic principles are based on (1) forced renal elimination of excess calcium by diuresis, (2) medicinal control of calcium metabolism by corticosteroids, indomethacin, mithramycin, and diphosphonate, (3) and hormonal control of calcium exchange by calcitonin. Five clinical cases are reviewed. No serious therapeutic problems were encountered. (11 Refs) (In GER)

18. HYPERCALCEMIA COMPLICATING SMALL-CELL CARCINOMA.

Hayward ML, Howell DA, O'Donnell JF, Maurer LH
Hitchcock Clinic, Hanover, NH, 03755
Cancer; 48(7):1643-1646 1981

Hypercalcemia is a common paraneoplastic syndrome complicating some varieties of lung cancer. It has rarely been reported with small-cell carcinoma of the lung. Seven cases of hypercalcemia complicating small-cell carcinoma of the lung are described; clinical features indicate that significant bone or bone marrow involvement is present in all cases. Parathormone assays were found to be generally in the normal range, though inappropriate for the level of hypercalcemia. (Author abstract) (17 Refs)

19. SOMATOSTATIN, GASTROINTESTINAL PEPTIDES, AND THE CARCINOID SYNDROME.

Long RG, Peters JR, Bloom SR, Brown MR, Vale W, Rivier JE, Grahame-Smith DG
Gastrointestinal Lab., St. Thomas' Hosp., London SE1 7EH, England
Gut; 22(7):549-553 1981

During a control infusion noradrenaline and alcohol each provoked carcinoid flushing in four of five patients and pentagastrin in two of five patients. When tetradecapeptide somatostatin was infused on another day no patient flushed at any time, even when 16 ug of either noradrenaline or pentagastrin were administered. Carcinoid flushing was not associated with release of gastrin or any of the other vasoactive or postprandially released gut regulatory peptides measured. In a sixth patient with severe prolonged carcinoid flushing, sc Des AA1,2,4,5,12DTrp8 somatostatin markedly reduced the incidence and severity of flushing for 2 days. Somatostatin is thus a potent inhibitor of carcinoid flushing, but no evidence has been found for the gut hormones measured to be mediators of flushing. (Author abstract) (21 Refs)

20. HORMONAL ASPECTS OF PARENTERAL NUTRITION DURING INTENSIVE THERAPY OF CANCER PATIENTS.

Sudzhian AV, Rozanova NB
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (8):77-79 1981

The effect of parenteral nutrition (PN) on the hormonal status was studied in 83 patients with cancer of the stomach. Pre- and postoperative PN decreased cortisol, glucagon, and growth hormone levels, and increased insulin level. (10 Refs) (In RUS)

21. OPERATIVE AND CHEMOTHERAPEUTIC MANAGEMENT OF MALIGNANT GLUCAGON-PRODUCING TUMORS.

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Surgery; 90(4):713-719 1981

Glucagon-producing tumors of the pancreas are among the rarest forms of islet cell tumors. Two patients are described in whom the characteristic dermatitis, glucose intolerance, wt loss, and anemia of the glucagonoma syndrome were due to a metastasizing islet cell carcinoma. In both, removal of the primary tumor with a distal pancreatectomy brought marked relief of all clinical symptoms for 1-and 2-yr periods. Because streptozocin, the usual chemotherapeutic agent for these tumors, is quite toxic and frequently unsuccessful, dimethyltriazenoimidazole carboximide (DTIC) was used for recurrence after operation. The first patient began taking DTIC when his rash reappeared and his immunoreactive glucagon (IRG) level rose to 6,000 pg/ml (normal, less than 200 pg/ml). Within 3 mo, his rash was gone, and IRG level was 75 pg/ml. The second patient developed a neoplastic gastrocolic fistula and was extremely emaciated. With DTIC, the fistula healed, and he gained wt and returned to work. His IRG level has decreased from 2,975 to 200 pg/ml. No side effects were noted during chemotherapy. Temporary palliation of malignant glucagon-producing neoplasms can be achieved by cytoreductive surgery. When the life-threatening symptoms of this syndrome recur, DTIC chemotherapy seems indicated because of its safety and effectiveness. (Author abstract) (13 Refs)

22. COMPARATIVE STUDIES ON THE KININ-FORMING SYSTEM IN THE BONE MARROW PUNCTATES AND IN THE PERIPHERAL BLOOD IN CASES OF CERTAIN HEMATOLOGICAL DISEASES.

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Arch Immunol Ther Exp (Warsz); 29(2):155-159 1981

Fibrinolysis time, kininase activity, and kininogen levels were analyzed in blood and bone marrow (BM) aspirates from 22 patients (9 women and 13 men) with chronic myelocytic leukemia (CML), 21 patients (4 women and 17 men) with chronic lymphatic leukemia (CLL), and 19 patients (10 women and 9 men) with hypochromic anemia (HA). Fibrinolysis time was significantly longer and kininogen content was lower in the BM than in the blood of CML and HA patients. Blood kininase was slightly reduced. In CLL, kininase activity was significantly lower in both blood and BM (68.1% and 68.0%, respectively). Differences in fibrinolytic activity and kininogen levels were not significant. Possible influences of granulocyte proteases on BM kininogen content and of lysosomal enzymes on blood kininase are discussed. (19 Refs)

EFFECTS ON NORMAL AND NEOPLASTIC CELLS AND TISSUES

23. GROWTH CONTROL OF PROSTATIC CARCINOMA CELLS IN SERUM-FREE MEDIA: INTERRELATIONSHIP OF HORMONE RESPONSE, CELL DENSITY, AND NUTRIENT MEDIA.

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Proc Natl Acad Sci USA; 78(9,part2):5673-5676 1981

Two established prostatic carcinoma cell lines have been grown in long-term culture in a defined medium (PFMR-4) free of serum, hormones, or growth factors. Growth of both lines in serum-free medium was population dependent. This cell-density requirement could be replaced by mitomycin C-inactivated feeder cells, homologous conditioned medium, or fetal bovine serum, but not by hormones or growth factors. The cells responded to these factors only at high density. The nature of this hormonal response was dependent on the kind of basal nutrient medium used. Growth in PFMR-4 with added insulin was more rapid than that in DME/F12 medium with any combination of hormones or growth factors and was substantially greater than growth in DME/F12 medium with insulin alone. The results demonstrate that whereas these two prostatic carcinoma lines (PC-3 and DU 145) do not require hormones for survival or growth, they do respond to certain hormones under appropriate conditions. These conditions include both the type of basal nutrient medium used and the population density. (Author abstract) (20 Refs)

24. MELATONIN INHIBITION AND PINEALECTOMY ENHANCEMENT OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS IN THE RAT.

Tamarkin L, Cohen M, Roselle D, Reichert C, Lippman M, Chabner B

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Cancer Res; 41(11,part1):4432-4436 1981

The effects of the pineal hormone, melatonin, and of pinealectomy on the incidence of mammary adenocarcinoma in Sprague-Dawley rats treated with 7,12-dimethylbenz(alpha)anthracene (DMBA) were investigated. Melatonin (2.5 mg/kg), begun on the same day as DMBA (15 mg) treatment and given daily in the afternoon for 90 days, significantly reduced the incidence of mammary tumors from 79% (control) to 20% (treated) (p less than 0.002). Rats pinealectomized at 20 days of age and treated with 7 mg of DMBA at 50 days of age had a higher incidence of tumors (88%) compared to control animals (22%). Fifteen mg of DMBA, which resulted in a higher incidence of tumors, reduced the difference between pinealectomized and control animals. Melatonin only partially reversed the effects of pinealectomy, reducing the incidence from 87% (pinealectomy alone) to 63% (pinealectomy plus melatonin); however, the tumor incidence was still lower (27%) in nonpinealectomized, melatonin-treated animals. Assessment of plasma prolactin, luteinizing hormone, follicle-stimulating hormone, estradiol, and cortisol in DMBA-treated tumor-free and tumor-bearing animals revealed a significantly lower plasma prolactin concentration [27 +-5 (SE)ng/ml] in melatonin-treated animals as compared to vehicle-treated animals [65 +-8 ng/ml]. The concentration of plasma prolactin was less in melatonin-treated, pinealectomized rats (55 +-10 ng/ml) as compared to vehicle-treated, pinealectomized animals (101 +-13 ng/ml). Other hormones were not affected by melatonin treatment. These data support the hypothesis that melatonin inhibits the development of DMBA-induced mammary tumors in the rat while removal of the pineal gland stimulates development of such tumors. Additionally, these experiments provide evidence that these effects may be mediated by a suppression of plasma prolactin levels. (Author abstract) (28 Refs)

25. CRUCIAL ROLE OF THYROID HORMONE IN X-RAY-INDUCED NEOPLASTIC TRANSFORMATION IN CELL CULTURE.

Guernsey DL, Borek C, Edelman IS
Dept. Physiology and Biophysics, Univ. Iowa Coll. Medicine, Iowa City, IA, 52242
Proc Natl Acad Sci USA; 78(9,part2):5708-5711 1981

Incubation of mouse embryo fibroblasts (C3H/10T1/2) in media depleted of thyroid hormone for 1 wk rendered the cell completely resistant to the transforming action of an x-ray dose, 4 grays, that yields transformation frequencies (no. foci per surviving cells) of approx 10(-3) in media supplemented with triiodothyronine (T3) (1 nM). Studies on the timing of the additions or removal of the hormone indicate that T3 was maximally effective when added 12 hr before irradiation and that progression from the time of irradiation to the appearance of foci (6 wk) was independent of the presence or absence of the hormone. The dependence of x-ray-induced transformation on the concentration of T3 in the medium was virtually the same as that for augmentation of Na+, K+ -ATPase activity. The latter effect was used as a measure of T3 induction of protein synthesis. A further indication of the involvement of protein synthesis in the process is the abolition of T3-and x-ray-dependent transformation by cycloheximide at a concentration (100 ng/ml) that inhibits 50% of protein synthesis. We propose that thyroid hormone induces the synthesis of a host protein that is an obligatory participant in x-ray-mediated transformation. (Author abstract) (17 Refs)

26. LONG-TERM ISOGRAFTS OF CULTURED FETAL MOUSE PANCREATIC ISLETS. THE ONCOGENIC EFFECTS OF STREPTOZOTOCIN AND THE PREVENTION OF DIABETIC RENAL COMPLICATIONS.

Mandel TE, Hoffman L, Carter WM
Walter and Eliza Hall Inst. Medical Res., Post Office Royal Melbourne Hosp., Victoria, 3050, Australia
Am J Pathol; 104(3):227-236 1981

Female CBA mice made diabetic with a single iv dose of streptozotocin (STZ) were either grafted with cultured fetal mouse pancreatic islets onto the splenic capsule, treated with insulin, or left untreated. An age- and sex-matched group of nondiabetic mice served as normal controls. All islet-grafted and most insulin-treated mice survived and had normal fasting blood glucose levels. By contrast, of the untreated diabetic mice, one died and the survivors showed poor wt gain. Light-microscopic examination of the islet isografts showed a progressive increase in graft size and beta-cell granulation over the 9-mo study period. Quantitative electron-microscopic examination of the kidney showed that, whereas the islet-grafted and nondiabetic control mice had similar glomerular capillary basement membrane (GCBM) thickness, the untreated diabetic and insulin-treated mice had markedly thickened GCBM. All STZ-treated mice developed diffuse hepatic dysplasia and, at later time points, some showed biliary hyperplasia, intrahepatic cysts, and occasionally nodular dysplasia. With increasing time after STZ, most mice developed renal adenomas. One untreated diabetic mouse also developed a solitary functional pancreatic beta-cell adenoma. STZ effects w ere not affected by treatment of diabetes. (Author abstract) (46 Refs)

27. DEVELOPMENT OF EXPERIMENTAL TUMORS IN THE OVARY OF A RAT AFTER TRANSPLANTATION INTO SPLEEN.

Yakushiji M, Imamura M, Masumoto R, Kato T
Dept. Obstetrics and Gynecology, Kurume Univ. Sch. Medicine, Kurume 830, Japan
Kurume Med J; 28(1):45-52 1981

Intrasplenic ovarian transplantation was performed in 222 female Wistar rats in order to observe morphological changes of the transplanted ovary over time and to study the influence of gonadotropin on tumor development. Of the 222 rats, 50 were treated with 50 IU of human chorionic gonadotropin (HCG) 3x/wk, 64 with 50 IU of PMS 3x/wk, 50 with both HCG and PMS, 34 were subjected to bilateral oophorectomy, and 4 were used as controls. No tumors developed until 25 wk after transplantation. After the 30th wk, tumors were seen in 78.8% of the transplantation group, 100% of the HCG-PMS group, 96.1% in the PMS group, and 100% of the HCG group. Tumors included theca cell tumors, theca-granulosa cell tumors, and granulosa-theca cell tumors. After wk 30, many of the transplanted ovarian grafts were enlarged and appeared grossly as tumors. After transplantation, the wt of the ovaries increased in all groups with the greatest increase in the PMS-only group. Follicle stimulating hormone (FSH) increased after castration, reached a peak after 2-4 wk, and remained high, while luteinizing hormone (LH) increased reaching a peak at 5 wk and remained higher than controls. In the tumor-producing groups, FSH decreased but LH did not change significantly. The results indicate that gonadotropin contributes to tumor production and that FSH also plays an important role. (17 Refs)

28. EPINEPHRINE DESENSITIZATION OF ADENYLATE CYCLASE FROM CYC- AND S49 CULTURED LYMPHOMA CELLS.

Green DA, Friedman JA, Clark RB
Graduate Sch. Biomedical Sciences, Univ. Texas Health Science Center at Houston, Houston, TX, 77025
J Cyclic Nucleotide Res; 7(3):161-172 1981

Specific beta-adrenergic desensitization of adenylate cyclase (AC) was characterized in the AC deficient lymphoma cell line cyc- and in the wild type S49 (WT). Cells were preincubated with (-)epinephrine (EN)plus 1.0 milliM thiourea and 0.1 milliM ascorbate or with thiourea and ascorbate alone. Both cyc- and WT cells were desensitized at the same rate by 1.0 uM EN during the first 10 min after treatment. After 60 min WT cells were 75% desensitized and cyc- cells 54% desensitized. Pretreatment for 18 hr with the beta-adrenergic agonist terbutaline produced EN-stimulated desensitization of 92% in WT compared with 48% in cyc-. Beta-adrenergic receptor levels were reduced in WT from 321 to 28 femtomoles (fmol)/mg protein and in cyc- from 580 to 438 fmol/mg protein. Both WT and cyc- were resensitized by propranolol, although WT did not recover full sensitization. Half max desensitization was produced in both cell types by 0.2-0.4 uM EN, and full desensitization by 10 uM EN. Apparently both WT and cyc- undergo rapid, reversible specific beta-adrenergic desensitization of AC that is independent of the G/F proteins of the adenylate cyclase complex. A slower desensitization occurs only in WT. (27 Refs)

EFFECTS OF ENDOGENOUS AND EXOGENOUS AGENTS ON NON-STEROID HORMONE ACTIVITY

29. RESTORATION OF PITUITARY PROLACTIN SYNTHESIS AND RELEASE BY THE ADMINISTRATION OF MORPHINE TO RATS BEARING A TRANSPLANTED PROLACTIN-SECRETING TUMOR.

Login IS, Nagy I, MacLeod RM
Dept. Neurology, Box 394, Univ. Virginia Sch. Medicine, Charlottesville, VA, 22908
Neuroendocrinology; 33(2):101-104 1981

Morphine sulfate (MS: 1.44 mg/day) and haloperidol (HP: 0.11 mg/day) were tested for their effects on pituitary prolactin (PRL) synthesis in female Wistar-Furth rats implanted with a PRL-secreting pituitary tumor (MtTW15). Anterior pituitary glands from untreated tumor-bearing rats incorporated 3H-leucine into newly synthesized 3H-PRL equivalent to 1,687 cpm/mg pituitary; of this amount, 657 cpm/mg was synthesized and released into the incubation medium. Constant infusion of MS or HP for 4 days using an osmotic pump caused a significant increase in synthesis (p less than 0.01) and release (p less than 0.01) of PRL. Pituitary glands from HP-treated rats had 3H-PRL synthesis and release rates equivalent to 5,870 and 2,487 cmp/mg, respectively; the corresponding values for MS-treated rats were 3,307 and 1,558 cmp/mg, respectively. HP, but not MS, treatment resulted in a significant increase in serum PRL levels. Probable mechanisms by which HP and MS affected pituitary hormone synthesis are discussed. (14 Refs)

30. EFFECT OF BROMOCRIPTINE, SOMATOSTATIN, AND OESTRADIOL-17BETA ON HORMONE SECRETION AND ULTRASTRUCTURE OF HUMAN PITUITARY TUMOURS IN VITRO.

Prysor-Jones RA, Kennedy SJ, O'Sullivan JP, Jenkins JS
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Acta Endocrinol (Copenh); 98(1):14-23 1981

The effect of bromocriptine and somatostatin on hormone secretion and the ultrastructure of human pituitary adenomas was studied in vitro. Prolactin secretion was inhibited by bromocriptine in 3 out of 10 prolactin-secreting tumors and in explants from two normal pituitaries. GH secretion was reduced by bromocriptine in four out of six GH-secreting adenomas but was not affected by the drug in the incubations of normal pituitaries. Somatostatin inhibited GH secretion in two out of five pituitary adenomas and the effect was comparable with that of bromocriptine. Incubation of prolactin-secreting adenomas with estradiol for a long as 24 days produced no change in hormone secretion. Examination of tumor ex plants by electron microscopy showed that somatostatin and bromocriptine produced accumulation of secretion granules but no changes in the secretory organelles. Long term bromocriptine treatment of 'nude' athymic mice bearing xenografts of human pituitary adenomas suppressed hormone secretion and produced some increase in secretion granules but there were no morphological changes in the secretory organelles or other vital structures of the adenoma cells. (Author abstract) (27 Refs)

31. THE STATE OF PITUITARY-THYROID SYSTEM IN RATS SUBJECTED TO PROLONGED INTERNAL IRRADIATION.

Dedov VI, Norets TA
Res. Inst. Medical Radiology, Obninsk, USSR
Radiobiologiia; 21(3):401-406 1981

To evaluate the potential after effects of diagnostic radionuclides, random-bred rats received single iv injection of 75Se-selenomethionine (total absorbed dose of 50 rads). Within different time periods after administration (from 1 wk to 18 mo) animals were sacrificed, and the pituitary and thyroid glands were subjected to histological and electron microscope examination. Determination of thyroxine concentration in the blood plasma showed marked stimulation of the thyroid function within the first 3 mo after radionuclide administration, followed by stable and severe inhibition of thyroid activity 6-18 mo later. The inhibition of the functional activity of thyroid was associated with the structural changes in the thyrocytes and with the decreased synthesis of thyroid stimulating hormone in the pituitary gland. (4 Refs) (In RUS)

32. ABNORMAL CALCIUM-REGULATED PTH RELEASE IN NORMAL PARATHYROID TISSUE FROM PATIENTS WITH ADENOMA.

Brown EM, Wilson RE, Thatcher JG, Marynick SP
Endocrine-Hypertension Unit, Brigham and Women's Hosp., 75 Francis St., Boston, MA, 02115
Am J Med; 71(4):565-570 1981

The regulation of parathyroid hormone (PTH) secretion by calcium was studied in normal and abnormal parathyroid tissue from five patients with a parathyroid adenoma. Dispersed cells were prepared from the adenoma and from a portion of a normal parathyroid gland and were incubated for 2 hr with varying concentrations of calcium. PTH release as a function of the concentration of calcium was determined by radioimmunoassay (C-terminal). Cells from the normal glands showed a lower set-point for calcium (the concentration of calcium causing half of the max inhibition of PTH release) than those from the adenomas in four of five cases. Moreover, both set-point and max PTH release at low concentrations of calcium were significantly lower in normal glands from patients with an adenoma than in normal glands from patients with normal calcium homeostasis (0.77 +-0.04 [SEM] versus 0.99 +-0.03 mM calcium and 3.4 +-0.43 versus 10.1 +-0.78 ng/10(5) cells/hr, respectively). These observations may explain, in part, the t ransient hypocalcemia frequently seen in patients after removal of a parathyroid adenoma. In addition, they suggest that the set-point for calcium and max PTH release in normal parathyroid tissue may be altered by prior exposure to chronic hypercalcemia or other physiologic variables. Finally, the 'normal' set-point that we have noted previously in parathyroid tissue from some patients with primary parathyroid hyperplasia may be inappropriately high for the hypercalcemia seen in those cases. (Author abstract) (17 Refs)

33. INSULIN SECRETION BY A TRANSPLANTABLE RAT ISLET CELL TUMOUR.

Sopwith AM, Hutton JC, Naber SP, Chick WL, Hales CN
Dept. Clinical Biochemistry, Univ. Cambridge, Addenbrooke's Hosp., Hills Rd., Cambridge CB2 2QR, England
Diabetologia; 21(3):224-229 1981

A transplantable rat islet cell tumor was studied as a possible large-scale model for insulin secretion. Stimulation and inhibition of insulin secretion by various agents were examined. Glucose (8.4-48 mM) did not stimulate secretion. Increased release of insulin was provoked by leucine (max response at 20 mM) and theophylline (max response at 5mM). Leucine and theophylline in combination produced a greater-than-additive effect. Insulin release was also stimulated by dibutyryl cyclic AMP. Presence of glucose, pyruvate, glutamate, and fumarate in the buffer resulted in accelerated response to stimulation. Insulin release was inhibited by sodium cyanide (1 mM), antimycin A (5 uM), 2,4-dinitrophenol (0.3 mM), and the presence of lanthanum, magnesium, or cobaltous ions, adrenalin, calmodulin, and somatostatin. Insulin release by islet cell tumor was thus shown to occur in response to specific stimuli and to depend on the cellular energy system. It apparently occurs by an exocytotic process similar to that occurring in normal islet cells; the tumor may therefore be used as a model for the insulin secretory process. (39 Refs)

34. RETINOIDS: NEW DEVELOPMENTS IN THEIR MECHANISM OF ACTION AS RELATED TO CONTROL OF PROLIFERATIVE DISEASES.

Sporn MB
Lab. Chemoprevention, Div. Cancer Cause and Prevention, NCI, Bethesda, MD
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

New evidence suggests that retinoids block proliferation induced by polypeptide hormones (PH) or hormone-like agents. Whether the antiproliferative effects of retinoids on epithelial cell differentiation involves modulation of the action of PH is unknown. Retinoids have been shown to have an antagonistic effect on proliferative PH in several disease states, especially malignancy. (15 Refs)

RECEPTOR/ BINDING SITES

35. STUDIES ON MELANOTROPIN (MSH) RECEPTORS OF MELANOPHORES AND MELANOMA CELLS.

Eberle AN
MRC Lab. Molecular Biology, Hills Road, Cambridge CB2 2QR, England
Biochem Soc Trans; 9(1):37-39 1981

The structure and receptor-site binding properties of alpha-melanotropin (a-MSH) were studied in frog melanophore and mouse melanoma cell systems. Both cell systems bound a-MSH in a similar manner. The hormone molecule contained two message sequences with the key elements -Phe-Arg- and -Lys-Pro-. The N-terminal part of the molecule had no melanotropic activity but potentiated the single or combined message sequences. (14 Refs)

36. LUTROPIN RECEPTORS IN NORMAL AND TUMOUR LEYDIG CELLS.

Cooke BA, Dix CJ, Magee-Brown R
Dept. Biochemistry and Chemistry, Royal Free Hosp. Sch. Medicine, Univ. London, 8 Hunter St., London WC1N 1BP, England
Biochem Soc Trans; 9(1):40-42 1981

Leydig cells from normal adult mouse and rat testes and a Leydig cell tumor can be separated into two cell populations (both containing lutropin receptors) which differ in density and steroidogenic responsiveness. The etiology of these cell types is unknown. They may reflect different phases in a cell cycle. Treatment with gonadotropin (lutropin or human choriogonadotropin) in vivo has been shown to result in the loss of lutropin receptors, a reduction in adenylate cyclase activity, and reduced steroidogenesis; treatment of rats with gonadotropin results in reduced sensitivity of Leydig cells to lutropin in vitro. Tumor cells of density 1.07 g/ml were exposed in vitro to lutropin (0.0, 10, 100, or 1,000 nanog/ml) and exhibited an initial increase in number of lutropin receptors. This reached a max in the controls after 2 hr and remained constant thereafter. All lutropin-treated cells showed decreased binding of choriogonadotropin after 1-2 hr incubation. Basal production of cyclic AMP initially reflected pretreatment with lutropin. Cyclic AMP rose sharply within 1 hr and returned to normal pretreatment levels by 4 hr. Reduction in binding of choriogonadotropin was inhibited by cycloheximide, which prevented lutropin-induced desensitization of adenylate cyclase activity. Results indicate that desensitization of Leydig cells can be induced in vitro, and loss of both lutropin receptors and adenylate cyclase activity occurs simultaneously; both processes depend on protein synthesis. (16 Refs)

37. GONADOTROPIC HORMONE BINDING TO HUMAN OVARIAN TUMORS.

Kammerman S, Demopoulos RI, Raphael C, Ross J
Dept. Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016
Hum Pathol; 12(10):886-890 1981

A variety of normal human ovarian tissues as well as benign and malignant human ovarian neoplasms have been examined in vitro for the presence of gonadotropin binding sites and gonadotropi n-stimulable cAMP production, in order to determine whether gonadotropic hormones have an effect on ovarian tumors. Binding of either FSH or hCG, or both, was demonstrated in several tumors from each of the histologic subgroups of primary ovarian tumors, including epithelial, sex cord-stromal, and germ cell types. Cyclic AMP stimulation was found in one tumor of sex cord-stromal origin, in two of epithelial origin, in two of germ cell origin, and in one tumor-like condition, pregnancy luteoma. Additional biochemical studies are needed to characterize receptor sites and to relate them to histologic features, growth behavior in vivo, and serum gonadotropin levels. (Author abstract) (15 Refs)

38. BETA2 RECEPTOR-MEDIATED STIMULATION OF FRIEND ERYTHROLEUKEMIA CELL GROWTH BY THYROID HORMONES.

Gauwerky CE, Bersch NL, Golde DW
Div. Hematology-Oncology, Dept. Medicine, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Exp Hematol; 9(8):821-828 1981

Thyroid hormones are known to enhance normal erythroid colony growth (CFUE) and this enhancement depends on a functional beta2-adrenergic receptor mechanism. We investigated the response of Friend cells to thyroid hormones, catecholamines, and other compounds influencing cellular cAMP activity. The thyroid hormones L-T3, L-T4, and 'reverse T3' stimulated erythroleukemia colony growth in a serum-substituted methylcellulose culture system with peak activity at 10(-7) M. Various beta-adrenergic compounds enhanced Friend leukemia colony growth; however, the alpha-adrenergic agonist phenylephrine was inactive. Dibutyl cyclic AMP and the phosphodiesterase inhibitor theophylline also enhanced Friend leukemia colony formation. Adrenergic antagonists with beta2 specificity abrogated the stimulatory effect of L-T3, L-T4, and of 'reverse T3' at equimolar concentrations. These experiments demonstrate that thyroid hormones, beta-adrenergic agonists, the phosphodiesterase inhibitor theophylline, and dbcAMP have a direct effect on the proliferation of Friend erythroleukemia cells. We conclude that thyroid hormones' action requires a functioning beta2-adrenergic receptor mechanism. Thyroid hormones directly modulate the growth of neoplastic erythroid cells in a manner consistent with their effects on normal erythropoiesis. (Author abstract) (31 Refs)

OTHER RELATED STUDIES

39. PANCREATIC POLYPEPTIDE. A REVIEW.

Lonovics J, Devitt P, Watson LC, Rayford PL, Thompson JC
(c/o Thompson) Dept. Surgery, Univ. Texas Medical Branch, Galveston, TX, 77550
Arch Surg; 116(10):1256-1264 1981

Pancreatic polypeptide (PP), a 36-amino acid peptide, may function as an important feedback inhibitor of pancreatic secretion after a meal. It arises from both islet and acinar cells of the pancreas. Release of PP by a meal, primarily protein, occurs in a biphasic manner. The first rapid relea se occurs as a result of vagal stimulation; the second, more prolonged rise (the so-called intestinal phase) occurs in response to hormonal stimulation, predominantly cholecystokinin. Plasma PP levels increase with age; PP levels are elevated above those of age-controlled normal subjects in diabetic patients and in some patients with pancreatic amine precursor uptake decarboxylase tumors. The value of plasma PP as a possible marker for pancreatic tumors is as yet unsettled but may be a valuable tool. (Author abstract) (136 Refs)

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HORMONES IN CANCER-RELATED BIOLOGY

Non-Steroid Hormones

SERIES CB24 No. 82/03

MARCH, 1982

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CHARACTERIZATION OF NON-STEROID

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HORMONES IN EXPERIMENTAL AND IN VITRO SYSTEMS

1. HYPERSECRETION OF AN ABNORMAL FORM OF FOLLICLE-STIMULATING HORMONE ASSOCIATED WITH SUPPRESSED LUTEINIZING HORMONE SECRETION IN A WOMAN WITH A PITUITARY ADENOMA.

Wide L, Lundberg PO
Dept. Clinical Chemistry, Univ. Hosp., S-750 14 Uppsala, Sweden
J Clin Endocrinol Metab; 53(5):923-930 1981

Pituitary tumors producing FSH have hitherto been reported only in males, all of whom have had normal or raised LH levels in serum. This report describes a female with a pituitary adenoma associated with supranormal serum levels of FSH. The FSH was also qualitatively abnormal when compared with FSH in the serum of other postmenopausal women, had a lower apparent mol wt on gel chromatography, and was less negatively charged, as shown by electrophoresis. The results of LRH tests and suppression tests with ethinyl estradiol indicated autonomy of the FSH-producing adenoma. The FSH level increased concomitant with tumor enlargement and decreased after surgical removal of the pituitary adenoma or pituitary irradiation. The serum level of the glycoprotein alpha-subunit was raised about 100-fold. Any free FSH beta-subunits were not detectable in serum. The abnormal FSH had antigenic sites in common with both the alpha- and beta-subunits of FSH. The LH level was extremely low, and there was no response to LRH tests or ethinyl estradiol treatment. After gel chromatography, a small amount of LH, corresponding to 1/50th of the av for the patient's age, was detected at the position for normal LH. There was no GH response to insulin-induced hypoglycemia, while the cortisol increase was normal. Thyroid and adrenal functions were normal. The PRL level was within the normal range and increased slightly after estrogen treatment. (Author abstract) (25 Refs)

2. GAMMA-MELANOTROPHIN-LIKE IMMUNOREACTIVITIES IN HUMAN PITUITARIES, ACTH-PRODUCING PITUITARY ADENOMAS, AND ECTOPIC ACTH-PRODUCING TUMOURS: EVIDENCE FOR AN ABNORMALITY IN GLYCOSYLATION IN ECTOPIC ACTH-PRODUCING TUMOURS.

Tanaka I, Nakai Y, Nakao K, Oki S, Fukata J, Imura H
Second Div., Dept. Medicine, Kyoto Univ., 54 Shogoin Kawaharacho, Sakyo-ku, Kyoto 606, Japan
Clin Endocrinol (Oxf); 15(4):353-361 1981

Using gel exclusion chromatography on Bio-Gel P-60, gamma-melanotropin-like immunoreactivity (gamma-MSH-LI) in three human pituitary glands, two ACTH-producing pituitary adenomas, and three ectopic ACTH-producing tumors (2 medullary thyroid carcinomas and 1 thymoma) was divided into one or two mol wt classes. The largest component eluted near the position of mouse 16K fragment and was designated big gamma-MSH-LI. This big gamma-MSH-LI was present in all samples. The second one, designated intermediate gamma-MSH-LI, eluted between the position of mouse 16K fragment and human ACTH, and was demonstrated only in two ectopic ACTH-producing tumors. No gamma-MSH-LI emerged at the elution position of synthetic gamma3-MSH. Affinity chromatography on concanavalin A-agarose revealed that a significant fraction (52-68%) of gamma-MSH-LI from human pituitary glands, ACTH-producing pituitary adenomas, and one ectopic ACTH-producing tumor bound to the column and was eluted with alpha-methyl-D-mannopyranoside. In two ectopic ACTH-producing tumors which contained big and intermediate gamma-MSH-LI, a relatively small fraction (27-35%) of gamma-MSH-LI bound to the column and was similarly eluted. These observations suggest that human gamma-MSH-LI is glycosylated and that there is an abnormality in the glycosylation of gamma-MSH-LI in some ectopic ACTH-producing tumors. (Author abstract) (22 Refs)

3. MALIGNANCY-ASSOCIATED HYPERCALCEMIA: EVALUATION WITH A CYTOCHEMICAL BIOASSAY FOR PARATHYROID HORMONE.

Goltzman D, Stewart AF, Broadus AE
Dept. Medicine, Royal Victoria Hosp., Montreal H3A 1A1, Canada
J Clin Endocrinol Metab; 53(5):899-904 1981

Employing a cytochemical assay initially developed for measuring parathyroid hormone (PTH), bioactivity was assessed in 33 patients with malignancies. Initial studies in vitro were consistent with a role for cAMP as a second messenger in the bioassay. Cytochemical bioactivity was increased in the peripheral plasma of 10 of 16 hypercalcemic patients with elevated nephrogenous cAMP excretion, and mean levels were 10-fold higher in these patients than in 17 normocalcemic or hypercalcemic patients with normal or suppressed nephrogenous cAMP excretion, respectively. Plasma bioactivity, serum calcium, and nephrogenous cAMP excretion all fell to normal in one patient after tumor resection, and cytochemical bioactivity was demonstrable in the tissue culture medium in which the neoplasm was maintained. Gel chromatographic analysis revealed that a major component of plasma bioactivity eluted before rather than with PTH-(1-84) in patients with malignancy in contrast with that in patients with primary hyperparathyroidism. The studies, therefore, demonstrate the capacity of the cytochemical bioassay to measure increased activity in patients with malignancy, hypercalcemia, and elevated nephrogenous cAMP excretion; suggest that the material responsible for the activity differs from PTH-(1-84); and provide a sensitive detector system for further analysis of this material and its role in the pathogenesis of this disease. (Author abstract) (22 Refs)

4. ECTOPIC HORMONE PRODUCTION BY ENDOCRINE TUMORS: LOCALIZATION OF HORMONES AT THE CELLULAR LEVEL BY IMMUNOCYTOCHEMISTRY.

Heitz PU, Kloppel G, Polak JM, Staub JJ
Dept. Pathology, Univ. Basel, Schonbeinstrasse 40, CH-4056 Basel, Switzerland
Cancer; 48(9):2029-2037 1981

Clinical and laboratory data, histologic, electron microscopic and immunocytochemical findings of the tumors of eight patients suffering from Cushing's syndrome and of one patient with hypercalcemia are described. The unlabeled antibody enzyme method was used for the detection of insulin, glucagon, somatostatin, pancreatic polypeptide, corticotropin, betalipotropin, calcitonin, parathyroid hormone, and gastrin. Ectopic Cushing's syndrome was caused by pancreatic endocrine tumors, medullary thyroid carcinoma, a bronchial a gastric and a thymic carcinoid, and a carcinoid of the mediastinum. Hypercalcemia in one patie nt was related to a pancreatic endocrine tumor. After surgery the clinical symptoms disappeared in two patients, but persisted or relapsed in five patients. ACTH-immunoreactivity could be demonstrated in six of eight tumors; calcitonin-immunoreactivity was found in the tumor of the patient suffering from hypercalcemia. ACTH-immunoreactivity could be localized to secretory granules by immunoelectron microscopy, and the presence of ACTH and beta-LPH in the same tumor cells could be shown in one pancreatic tumor. A combination of production of orthotopic and ectopic hormones was found in one, and secretion of two ectopic hormones was detected in another pancreatic endocrine tumor. (Author abstract) (41 Refs)

5. IMMUNO-CYTO-CHEMICAL STAINING OF MID-GUT CARCINOID TUMOURS WITH SEQUENCE-SPECIFIC GASTRIN ANTISERA.

Wilander E, El-Salhy M
Dept. Pathology, Univ. Uppsala, P.O. Box 553, S-751 22 Uppsala, Sweden
Acta Pathol Microbiol Scand [A]; 89(4):247-250 1981

Twenty typical mid-gut carcinoid tumors were examined for the presence of gastrin immuno-reactivity to antisera specific to the C-terminal pentapeptide or to the mid-portion of gastrin-17. Pentagastrin immuno-reactivity was found in seven cases, and in one of these reactivity to antiserum against the mid-portion of gastrin-17 was also observed. The results are in accordance with the previous observation that argyrophil tumor cells are present in mid-gut carcinoid tumors and may explain why peptic ulcer disease is sometimes seen in association with the carcinoid syndrome. (Author abstract) (12 Refs)

6. RADIOIMMUNOLOGICAL DETERMINATION OF INSULIN-LIKE GROWTH FACTORS I AND II IN NORMAL SUBJECTS AND IN PATIENTS WITH GROWTH DISORDERS AND EXTRAPANCREATIC TUMOR HYPOGLYCEMIA.

Zapf J, Walter H, Froesch ER
Metabolic Unit, Dept. Medicine, Univ. Hosp., CH-8091 Zurich, Switzerland
J Clin Invest; 68(5):1321-1330 1981

Serum levels of immunoreactive insulin-like growth factors (IGF) I and II were determined by a modified IGF I and a new IGF II radioimmunoassay in normal children and adults, and in patients with acromegaly, isolated growth hormone deficiency, and extrapancreatic tumor hypoglycemia. Serum samples were gel filtered by a simple routine procedure at acidic pH to dissociate and separate IGF from the IGF carrier protein. Mean immunoreactive IGF I levels (+- SD; corrected for crossreactivity of IGF II) were 193 +-58 ng/ml in normal adult subjects, 712 +-245 ng/ml in acromegalic patients and 24 +-14 ng/ml in patients with isolated growth hormone deficiency. The lack of growth hormone alone, irrespective of an otherwise normal hormonal status, appears to be responsible for the drastic decrease of IGF I levels. Oversecretion of growth hormone does not increase the levels of immunoreactive IGF II: mean levels (+- SD; corrected for crossreactivity of IGF I) in normal and acromegalic subjects were virtually identical (647 +-126 and 641 +-189 ng/ml, respectively). Apparently, normal growth hormone levels stimulate IGF II production already maximally. However, in growth hormone deficiency immunoreactive IGF II is significantly decreased (252 +-99 ng/ml). Thus, IGF II, like IGF I, is growth hormone dependent. But in contrast to IGF I, the growth hormone dependence of IGF II seems to become apparent only at subnormal growth hormone levels. In normal children IGF I is age dependent: it is low in newborn cord sera (51 +-20 ng/ml) and gradually rises into the adult range with increasing age. At the onset of and during puberty mean IGF I levels lie above prepubertal values. In contrast, IGF II levels in normal children are independent of age and pubertal stage beyond the first yr of life, whereas newborns have significantly lower IGF II values. Hypoglycemia resulting from extrapancreatic tumors is not associated with increased immunoreactive IGF I or II levels. IGF I is decreased in most of the sera (mean level +- SD: 56 +-39 ng/ml) whereas IGF II lies in the normal range (556 +-195 ng/ml). (Author abstract) (31 Refs)

7. DEGRADATION DURING STORAGE OF HIGH MOLECULAR WEIGHT IMMUNOREACTIVE INSULIN (HWIRI) AND PROINSULIN (PLC) IN EXTRACTS OF BENIGN INSULINOMAS AND ADJACENT PANCREATIC TISSUE.

Villaume C, Beck B, Pointel JP, Drouin P, Debry G
Groupe de Nutrition et de Dietetique, INSERM U. 59, 40 rue Lionnois, 54000 Nancy, France
Horm Metab Res; 13(9):528-529 1981

Gel filtration assay for high mol wt immunoreactive insulin (HWIRI), proinsulin (PLC), and immunoreactive insulin (IRI) in specimens of islet cell adenoma was conducted immediately after pancreatectomy and extraction and after 15-day storage at-20 C. Progressive decrease of PLC and HWIRI as a percentage of IRI content was observed. The findings are indicative of HWIRI and PLC degradation during storage. (8 Refs)

8. IMMUNOHISTOCHEMICAL EVIDENCE OF PEPTIDE HORMONES IN ENDOCRINE TUMORS OF THE RECTUM.

Alumets J, Alm P, Falkmer S, Hakanson R, Ljungberg O, Martensson H, Sundler F, Tibblin S
Dept. Histology, Univ. Lund, Biskopsgatan 5, S-223 62 Lund, Sweden
Cancer; 48(11):2409-2415 1981

Twenty-five endocrine tumors of the rectum (rectal carcinoids) were examined immunohistochemically for various pancreatic and gut neurohormonal polypeptides. Twenty-one of the tumors were found to contain cells displaying pancreatic polypeptide (PP), glucagon, somatostatin, insulin, substance P, enkephalin or beta-endorphin immunoreactivity. At least 11 of the tumors contained more than one peptide hormone. In some of the tumors PP cells made up the major cell population, in others the glucagon cells constituted the majority. Only four of the tumors contained 5-hydroxytryptamine. Rectal endocrin e tumors seem unique among gut endocrine tumors in that they may store immunoreactive enkephalin, beta-endorphin and even insulin. None of the patients displayed the carcinoid syndrome; symptoms were usually vague and uncharacteristic. In many cases the tumor was found at routine examination. (Author abstract) (37 Refs)

9. CONCANAVALIN A AFFINITY MOLECULAR VARIANTS OF HCG AND ITS SUBUNITS IN SERUM OF PATIENTS WITH TESTICULAR TUMOURS (MEETING ABSTRACT).

Mann K, Lamerz R, Karl HJ
Department of Medicine III, University of Munich, Munich, W. Germany
Oncodev Biol Med; AbstractsBook,1:52 1981

Molecular variants of human chorionic gonadotropin (hCG) have been shown in female patients with trophoblastic diseases. In contrast, the heterogeneity of hCG and its subunits is unclear in patients with non-seminomatous germ cell testicular tumors (NSGCT). We studied the binding of hCG and hCG subunits to Concanavalin A (Con A) sepharose in a selected group of 7 patients with elevated serum levels of hCG and its subunits. HCG, hCG-beta and hCG-alpha were measured by specific radioimmunoassays and identified additionally by gel chromatography. Serum samples of 0.1 ml were applied on a 2 ml Con A sepharose column; not bound fractions were eluted with 0.15 M phosphate buffered saline (PBS), pH 7.5 containing 1% bovine serum antigen, bound fractions with 0.15 M PBS containing 0.2 M methyl-alpha-D-glucopyranoside. HCG, hCG-beta and hCG-alpha in serum from patients with NSGCT showed 22%, 45% and 30% Con A-non-reactive material respectively. The percentage of Con-A-non-reactive hCG, hCG-beta and hCG-alpha in pregnant serum was 0%, 49% and 6%, in purified preparations of hCG (CR 115), hCG-beta (CR 115 beta) and hCG-alpha (CR 117 alpha) 0%, 9% and 0%. Thus, Con A-non-reactive variants of hCG and hCG-alpha were discovered selectively in patients with NSGCT. Our data indicate differences in the carbohydrate moiety of hCG and hCG-alpha in sera of pregnant and cancer patients. (no Refs)

10. INCIDENCE OF HCG SUBUNITS IN PATIENTS WITH HCG-POSITIVE NONSEMINOMATOUS TESTICULAR GERM CELL TUMORS (MEETING ABSTRACT).

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Acta Endocrinol [Suppl]; 96(240):80 1981

Human chorionic gonadotropin (HCG) determinations in serum are widely accepted to be useful as tumor markers in testicular cancer. Most anti-hCG-beta antisera available are sufficiently specific with respect to their cross-reactivity with pituitary hormones, but the interference of hCG subunits in heterologous hCG-beta radioimmunoassays is poorly explored. In order to evaluate the incidence of hCG subunits in sera with elevated hCG levels hCG, hCG-beta, and hCG-alpha were determined simultaneously using specific assays, 125I-hCG, anti-hCG-beta Serono, 125I-hCG-beta, anti-hCG-beta Union Carbide and 1 25I-hCG-alpha, anti-hCG-alpha 'Irmi'. Data of subunit determinations were corrected respecting the 2.2% cross-reactivity of hCG in the homologous hCG-beta assay and 6.4% in the alpha-assay. HCG and hCG-alpha levels were compared in 40 patients with nonseminomatous germ cells tumors. hCG, hCG-beta, and hCG-alpha in 25. The control group consisted of male patients without neoplastic, chronic inflammatory, thyroid or renal diseases. Labeled hCG, hCG-beta and hCG-alpha donated from NIAMD, was cochromatographed as an internal standard. Blue dextran, 125I and labeled hormones were also gel filtered in separate experiments for calibration. Five (20%) out of 25 hCG positive patients showed elevated hCG-beta levels and of 40 patients 4 (10%) had elevated hCG-alpha levels. Definite proof of subunit secretion was performed in 3 cases by gel chromatography of the patients' sera. In one patient immunoreactive hCG-beta showed two peaks, corresponding to 125I-hCG-beta and a high molecular from. HCG-alpha eluted in an identical position with 125I-hCG-alpha. These data demonstrate that hCG subunit secretion in patients with elevated hCG levels is not a negligible rare event and support our proposal that, for routine purposes, a hCG assay is preferable, which makes it possible to determine hCG and hCG-beta simultaneously on parallel standard curves, standardized with the 2nd International Reference Preparation of hCG. (no Refs)

11. ENDOCRINE ACTIVITY IN CHORIONIC TUMOR CELLS (MEETING ABSTRACT).

Tsukahara Y, Nakamura H, Noda M, Fujii T, Dobashi K, Tsubata K, Takagi S
Department of Obstetrics and Gynaecology, Nihon University, School of Medicine, Itabashi-ku, Tokyo, Japan
Obstetric and Gynaecology: 8th Asian Congress, October 25-31, 1981, Melbourne, Australia Asia and Oceania Federation of Obstetricians and Gynaecologists 352 pp., 1981.

Our present study involves the immunohistochemical comparison of the localization of hormones in normal pregnancies, hydatidiform moles, destructive moles and choriocarcinomas. In moles and destructive moles in the area of villous structures, and in the marginal areas of choriocarcinomas as well as in the villous structures in normal pregnancies, we were able to identify human chorionic gonadotropin (hCG), its alpha and beta subunits, and human prolactin (hPL) in 'S' cells, but were unable to find them in 'L' cells. In the decidua and myometrium, we found clusters and scattered separate cells which were oval to spindle-shaped with weakly basophilic cytoplasm and single nuclei. Other large cells identified as trophoblasts had weakly basophilic cytoplasm and were multinucleate. Both types of cells were evaluated for the presence of hormones. In hydatidiform moles, we found hCG and hPL; in destructive moles, hCG, its alpha and beta subunits, and hPL in close correlation with the plasma findings. Choriocarcinoma showed the presence of all hormones evaluated and in metastatic lesions, the 'S' cells showed the presence of hCG and its alpha and beta subunits. The normal pregnancies revealed only the presence of hPL. Thus, in this investigation, we were able to discern various differences in hormonal distribution when comparing the basal plate trophoblasts of normal pregnancies with those from various chorionic tumors. (no Refs)

12. CHARACTERIZATION OF A SMALL MOLECULAR SIZE URINARY IMMUNOREACTIVE HUMAN CHORIONIC GONADOTROPIN (HCG)-LIKE SUBSTANCE PRODUCED BY NORMAL PLACENTA AND BY HCG-SECRETING NEOPLASMS.

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J Clin Endocrinol Metab; 53(5):1014-1020 1981

Urine obtained from normal pregnant women as well as from patients with hCG-secreting tumors frequently contains native hCG and free hCG subunits when separated on Sephadex G-100. In addition, a small amount of an immunoreactive, hCG-like, low mol wt substance is usually observed in those chromatograms and represents less than 1% of the total immunoreactive hCG present. Two patients with widely metastatic hCG-secreting tumors excreted disproportionately large quantities of that low mol wt substance, and that observation raised the possibility that this substance was a secretory and not a degradative product of the hCG molecule. The small immunoreactive hCG-like substance was subsequently characterized immunologically, biologically, and physically. The hCG fragment displayed a biphasic dose-response line in a homologous hCG RIA. The slope of the upper portion of the dose-response line was equal to that for native hCG, but the slope of the lower component of the dose-response line was significantly different from that for hCG. The immunoreactive hCG substance cross-reacted with hCGbeta but not with either hCGalpha or hCGbeta carboxyl-terminus. The small molecular size immunoreactive hCG-like substance bound to Concanavalin A-Sepharose 4B and eluted with 0.2 M alpha-D-methyl glucopyranoside, contained no significant intrinsic biological activity when tested in the in vitro Leydig cell bioassay and also failed to compete with labeled hCG for specific ovarian LH/hCG receptors. Consequently, that small urinary immunoreactive hCG substance behaved neither as a hCG agonist or antagonist. It exhibited a plasma half-life of 4.5 min when the appropriate Sephadex G-100 fractions were injected into immature female rats. The small molecular size immunoreactive hCG-like substance may be a secretory or breakdown product of hCG-secreting cells. (Author abstract) (26 Refs)

13. FALSE-POSITIVE AND FALSE-NEGATIVE ALPHA-FETO PROTEIN AND HUMAN CHORIONIC GONADOTROPIN ASSAYS IN TESTICULAR CANCER: A DOUBLE BLIND STUDY.

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Cancer; 48(10):2279-2281 1981

The rates of false-positive and false-negative serum alphafeto protein (AFP) and human chorionic gonadotropin (HCG) determinations in 50 patients with testicular cancer utilizing assays from a reference laboratory were studied. Seven (14%) of 50 patients had false-positive and 1 (2%) of 50 had false-negative serum HCG determinations. Although 6 (12%) of 50 of serum AFP determinations showed false-positive results; no false-negative rates were encountered for serum AFP. Utilizing simultaneous measurements of serum HCG and luteinizing hormone (LH) measuring urinary HCG by a highly specific carboxyl-terminal assay, one may rule out false-positive occurrences of serum HCG in patients with testicular cancer. This double-blind study also confirmed the need for correlating the clinical status of the patients with elevated serum AFP or HCG in patients with testicular cancer before embarking on any therapy. (Author abstract) (6 Refs)

CLINICAL, DIAGNOSTIC AND PROGNOSTIC STUDIES

14. ORAL CONTRACEPTIVE EXPOSURE OF AMENORRHEIC WOMEN WITH AND WITHOUT PROLACTINOMAS.

Jones JR, Kemmann E, Norwood PK
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Int J Gynaecol Obstet; 19(5):381-387 1981

Extent of prior oral contraceptive (OC) used by women with prolactinomas is compared to that of other women with secondary amenorrhea. Ninety-three of 126 women with secondary hypothalamic-pituitary amenorrhea were evaluated for serum prolactin (PRL), by sella tomography, menstrual history, and OC usage and divided into three groups. Results for 26 patients (Group A) showed prolactinoma and hyperprolactinemia indicated by elevated PRL concentrations (greater than 30 nanog (ng)/ml) and radiographic abnormalities of sella turcica. Results for 26 additional patients (Group B) revealed idiopathic hyperprolactinemia only indicated by PRL levels greater than 30 ng/ml and normal tomographies of the sella. Forty-one patients (Group C) had normoprolactinemia indicated by PRL levels less than 20 ng/ml and normal tomographies of the sella. Duration of OC exposure ranged from none to greater than 12 mo. Evaluation for 'post pill amenorrhea' in OC exposed patients revealed 9, 11, and 15, in Groups A, B, and C, respectively. These proportions were not determined to be significant. The results suggest that nonovulatory patients are likely candidates for OC therapy. Patients with prolactinomas apparently do not differe in the extent of OC exposure from other specified groups of amenorrheic patients. (22 Refs)

15. PART II: HYPERPROLACTINEMIA - DIAGNOSIS AND MANAGEMENT.

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J Med Soc NJ; 78(11):743-747 1981

Efficacy of radioimmunoassay measurement of serum prolactin (PRL) level for differential diagnosis between idiopathic hyperprolactinemia and pituitary prolactinoma is discussed. It was emphasized that the patients with microadenomas should be followed up with serum PRL levels every 6 mo, and that surgery should be performed only if there is an evidence of lesion progression. (48 Refs)

16. VALIDITY OF HYPOTHALAMIC-PITUITARY TESTING IN HYPERPROLACTINEMIA: PROLACTIN RESPONSES TO INSULIN HYPOGLYCEMIA AND ARGININE.

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Am J Obstet Gynecol; 141(5):556-561 1981

The release of prolactin (PRL) following insulin tolerance testing (ITT) and arginine infusion was studied in four groups of women: normal volunteers, amenorrheic women with normal PRL levels, and hyperprolactinemic women with and without roentgenographic evidence of pituitary adenoma. Women with normal serum PRL concentrations were found to have an increase in peripheral PRL after both testing modalities. Hyperprolactinemic women, whether or not there was evidence of a pituitary adenoma, did not appear to have a PRL response to either of these tests. Based on the percent change of PRL over basal values, there was a significant difference between the euprolactinemic and hyperprolactinemic groups (p less than 0.01 for insulin and p less than 0.05 for arginine). Our data indicate that in women with hyperprolactinemia neither ITT- nor arginine-induced PRL release can be utilized to discriminate between the presence and absence of an adenoma. This poor PRL response to ITT and arginine in the hyperprolactinemic patients could be the result of hypothalamic dysfunction. (Author abstract) (16 Refs)

17. EFFECT OF CYPROTERONE/ACETATE (SH-714) ON PLASMA PROLACTIN IN PATIENTS WITH PROSTATIC CANCER.

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Urol Res; 9(5):245-247 1981

Plasma prolactin (PR) levels were measured by radioimmunoassay in 10 prostatic cancer patients (age 50-78 yr) treated primarily with cyproterone acetate (CA: 300 mg/wk). Orchiectomy was not performed. Pretreatment PR levels were av 7.01-9.50 nanog (ng)/ml. The levels did not increase significantly during the first 5 mo of treatment, but they were significantly elevated by mo 6 to av 15.93 ng/ml (p less than 0.05). However, the effect of CA was less pronounced than that of estrogens. (18 Refs)

18. BROMOCRIPTINE AS PROPHYLACTIC THERAPY IN PROLACTINOMA DURING PREGNANCY.

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Fertil Steril; 36(4):524-526 1981

Eight infertile patients with radiologic evidence of pituitary tumor (6 macro-, 2 microadenoma) and prolactin (PRL) secretion above 100 nanog (ng)/ml, who wished to conceive, were treated with bromocriptine, (BR) 2.5-10.0 mg daily. Dose selected was that which was necessary to maintain morning PRL level at less than 20 ng/ml and to induce ovulatory menstrual cycles. Conception occurred in all cases within 8-56 wk of therapy. In four cases, BR was continued throughout the pregnancy and puerperium. All delivered a healthy male child (2,500-3,725 g), one by cesarean section. Infants born to four mothers who received BR throughout pregnancy showed no abnormalities and no respiratory distress. There was no sign of tumor enlargement during gestation in any case. There were no changes in visual fields or polytomography. Those mothers not treated with BR after delivery nursed their infants for at least 7 mo. One of four who continued BR, 5 mg/day, successfully breast-fed her infant. (8 Refs)

19. IMPAIRED PITUITARY RESPONSE TO BROMOCRIPTINE SUPPRESSION: REVERSAL AFTER BROMOCRIPTINE PLUS TAMOXIFEN (MEETING ABSTRACT).

Volker W, Gehring WG, Zur Muhlen AV
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Acta Endocrinol [Suppl]; 96(240):71 1981

The present study was undertaken on the assumption that bromocriptine plus tamoxifen might have a synergetic effect in previously resistant cases of prolactinoma to bromocriptine monotherapy. Twelve women aged 16 to 54 were tested. Two of them were unable to take bromocriptine because of severe side-effects, the others were under longterm bromocriptine therapy. Nine women had sellar or suprasellar enlargement, five of them having undergone incomplete surgical resection. The others had normal sella tomograms, but suppression was poor or impossible. Ten women continued taking bromocriptine, but additionally received tamoxifen 10 mg bid. Blood samples were taken before the beginning of combined therapy and one of four wk later. Prolactin (PRL), luteinizing hormone, follicle-stimulating hormone, estradiol and progesterone were determined by radioimmunoassay. The two women who had previously been unable to take bromocriptine were able to accept it in conjunction with tamoxifen. The combination with tamoxifen resulted in a marked suppression of PRL in six out of ten patients. In four cases there was no effect at all. In the three women with normal sella, PRL was suppressed to normal values. In the cases with sellar or suprasellar tumors the addition was successful in three, unsuccessful in four. No correlation was found between this effect and the extent of the tumor. In both women who tolerated bromocriptine when tamoxifen was added, PRL was suppressible. One woman conceived shortly after the combined therapy had been started. In six women spontaneous bleedings occurred, only in four of them had PRL been suppressed sufficiently. Basal body temperature curves became normal in three women, galactorrhea ceased in five. One woman reported a marked improvement of libido. The suppressive effect of bromocriptine on PRL secretion is enhanced by addition of tamoxifen in most cases of adenomatous hyperprolactinemia. Side-effects of bromocriptine are considerably improved by tamoxifen. (6 Refs)

20. ENDOCRINE EVALUATION OF PITUITARY ADENOMA TREATMENT (MEETING ABSTRACT).

Karlberg BE, Hjelm H, Nilsson OR, Tegler L

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Acta Neurochir; 56(1/2):117 1981

Clinical and biochemical evaluation was performed in about 110 patients treated for pituitary tumors during the last 15 yr at our hospital. After evaluation of clinical symptoms and signs of endocrine dysfunction we have applied a standardized test battery consisting of a stimulation test with 200 ug thyroliberin (TRH) and 100 ug gonadoliberin (LHRH) iv with measurements every 15 min for 120 min of serum concentrations of thyroid-stimulating hormone, prolactin, follicle-stimulating hormone, luteinizing hormone, and, in selected cases, human growth hormone (HGH), and basal concentrations of T4 and T3. Two days later a significant hypoglycemia has been induced by 0.1-0.2 IU insulin/kg body wt iv, and samples have been drawn for analysis of serum concentrations of cortisol, HGH, prolactin, and, in selected cases, ACTH. Seventy-one patients were operated on by the transcranial approach. Thirty-two of these patients had preoperative endocrine insufficiency, and another 11 developed insufficiencies postoperatively, mostly patients with large tumors. Thirty-nine patients were treated by the transsphenoidal approach. They were admitted to surgery mostly for endocrine hyperfunction, which was cured in six patients with acromegaly. Amenorrhea/oligomenorrhea was normalized in 11 out of 16 women, and galactorrhea disappeared in 7 out of 8 patients with prolactinoma, although only 8 out of 20 had normal prolactin concentrations postoperatively. Two of the patients who underwent transsphenoidal operations developed postoperative endocrine deficiencies. In the patients with intrasellar 'microadenomas' the final endocrine assessment can be made six wk after surgery. In about half of the patients with residual elevated concentrations of prolactin, bromocryptine has been given with further improvement of clinical symptoms and decreasing prolactin concentrations. (no Refs)

21. IMMEDIATE ENDOCRINE CHANGES FOLLOWING REMOVAL OF HYPERSECRETING PITUITARY ADENOMAS (MEETING ABSTRACT).

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Acta Neurochir; 56(1/2):121 1981

During the last yr and a half we have approached 45 intrasellar tumors by the transsphenoidal approach according to Cushing, Guiot, and Hardy, but with their method modified by per-operative 'mini-gas' cisternography. Of the 45 tumors, 29 secreted prolactin, 10 growth hormone, 1 ACTH, and 2 thyroid stimulating hormone. Two were non-secreting. In all patients sequential blood samples were drawn during and following surgery for determination of serum levels of prolactin, growth hormone, thyroid stimulating hormone, follicle stimulating hormone, luteinizing hormone, triiodothyronine, thyroxin, estradiol, as well as ACTH. The plasma level of the hormones hypersecreted from the tumors fell according to an exponential course, allowing calculation of kinetic characteristics of the removal of some anterior pituitary lobe hormones from plasma in humans. The data from the hormone laboratory can be used to evaluate the quality of surgery regarding quantity of tumor removal and preservation of pituitary function. (no Refs)

22. A CYPROHEPTADINE-REVERSIBLE DEFECT IN ACTH CONTROL PERSISTING AFTER REMOVAL OF THE PITUITARY TUMOR IN CUSHING'S DISEASE.

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N Engl J Med; 305(21):1244-1248 1981

Two phases of cortisol feedback suppression of ACTH were studied in nine patients who had adrenalectomy for Cushing's disease and in five hypoadrenal patients (controls). Among the nine patients, four had been treated by adrenalectomy alone and presumably had ACTH-secreting pituitary tumors, and the five others were studied greater than 2 yr after transsphenoidal removal of an ACTH-secreting microadenoma. Cortisol (CTS; 100 mg, iv, in 120 min) was infused 24 hr after the last po dose of cortisone. After the first cortisol infusion, cyproheptadine (CYH; 24 mg/day, po for 7 days) was given. CTS infusion was repeated 2 hr after the last dose of CYH and 24 hr after the last dose of cortisone. After 30 min of CTS infusion, plasma ACTH fell 28.0 +-10.1% (P less than 0.01) in the hypoadrenal control patients, but only 2.7 +-2.6% (P less than 0.01) in the nine patients treated by adrenalectomy. In the nine patients, the fall in ACTH after 30 min of CTS infusion was significantly greater after CYH (24.4 +-4.8%, P less than 0.005) than before. This enhanced negative feedback was similar in both groups of patients. After CYH was given, CTS levels during the second infusion were similar in patients and controls. The results suggest that higher centers may have a role in the pathophysiology of Cushing's disease. (29 Refs)

23. SOMATOMEDIN C IN TREATED ACROMEGALY: POOR CORRELATION WITH GROWTH HORMONE AND CLINICAL RESPONSE.

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J Clin Endocrinol Metab; 53(5):931-934 1981

To determine the usefulness of commercially available somatomedin C levels in the evaluation of the treatment of acromegaly, 15 patients were tested at 0.25-15.4 yr after onset of therapy. Clinical response, as determined by a numerical scoring system, was compared with RIA of GH and somatomedin C. Symptomatic response was poorly correlated with somatomedin C ($r = 0.033$) as well as with GH ($r = 0.24$). The correlation of GH and somatomedin C was also poor ($r = 0.46$, P greater than 0.05). Eighty-three percent of patients with clinical improvement had GH less than or equal to 10 ng/ml, 50% had GH less than or equal to 5 ng/ml, while 42% had somatomedin C less than or equal to 3.0 U/ml. All patients who were evaluated at 1 yr or less after therapy had elevated somatomedin C levels with normal or near normal GH values. In contrast only 2 of 11 patients evaluated at more than 1 yr after therapy had a mild persistence of somatomedin C elevation with normal GH levels. Determination of somatomedin C costs more than GH determinations and appears to offer no apparent advantage over GH in following patients treated for acromegaly. (Author abstract) (18 Refs)

24. OVARIAN FAILURE FOLLOWING CYTOTOXIC THERAPY (MEETING ABSTRACT).

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Abstracts of the Annual Scientific Meeting, February 8-12, 1981, Wellington, New Zealand. The Royal Australasian College of Physicians (Preprinted from Aust NZ J Med 11(3); 1981) 21 pp., 1981.

The 12 women in child-bearing age (15-40 yr) attending the Hematology clinic with acute and chronic leukemia. Hodgkin's disease and Non-Hodgkin lymphoma, were studied retrospectively for evidence of cytotoxic induced ovarian failure. Seven women were considered to have ovarian failure with reduced or absent menses, hot flushes, decreased libido, depression and irritability and raised gonadotropin (follicle-stimulating hormone (FSH), and luteinizing hormone (LH)) levels. Three women showed evidence of partial ovarian failure and only two women had normal ovarian function. Many of the affected women commented on strained personal relationships. Four women were given estrogen/progesterone replacements with immediate cessation of menopausal symptoms, the onset of monthly withdrawal menstruation and a return to their normal sense of well-being. Gonadotropin levels including FSH returned to normal. Cytotoxic induced gonadal failure has been recognized for many yr but the implications of this failure on the women's personal lives has been overlooked and very little attention has been paid to replacement hormonal therapy. Furthermore, menopausal symptoms may occur shortly after the onset of cytotoxic treatment, at a time when the women are still adjusting to the reality of their life-threatening disease. A wide range of cytotoxic drugs had been given to our patients but the daily use of aklylating agents appears to carry the highest risk of gonadal damage. (no Refs)

25. CEA, AFP, FSH, LH, HCG-B AND PRL VALUES IN THE SERUM OF UTERINE CERVICAL CANCER PATIENTS (MEETING ABSTRACT).

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Obstetrics and Gynaecology: 8th Asian Congress, October 25-31, 1981, Melbourne, Australia. Asia and Oceania Federation of Obstetricians and Gynaecologists 352 pp., 1981.

One hundred and four out of 224 (46.43%) uterine cervical cancer patients showed elevated carcinoembryonic antigen (CEA), 31 out of 222 (13.96% patients elevated luteinizing hormone (LH), 23 out of 220 (10.45%) patients elevated follicle stimulating hormone (FSH), 78 out of 216 (36.11%) patients elevated prolactin, 6 out of 216 (2.78%) patients elevated alpha-fetoprotein (AFP) and 15 out of 224 (6.70%) patients elevated human chorionic gonadotropin (hCG-b). Only CEA showed a correlation with the size of the primary tumor, and stage of the disease, and also possessed a clinical significance in detection of recurrence. High hCG-b values seems to be somewhat related to poor prognosis. A high PRL value also is of some clinical significance, however, not definite. AFP, FSH and LH seem less significant in prognostication. These findings will be illustrated with some particular cases. (no Refs)

26. HORMONE MARKERS FOR CANCER.

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Clinical Endocrinology Branch, Natl Inst. Arthritis, Metabolism, and Digestive Disease, Bethesda, MD
Med Times; 109(5):37-39 1981

Hormones that serve as simple blood tests for endocrine and nonendocrine cancers are reviewed. Choriocarcinoma can now be detected at a very early stage by sensitive radioimmunoassays for human chorionic gonadotropin (HCG); the greater than 75% cure rate reported for pregnancy-associated choriocarcinoma has been largely attributed to this hormone marker. Similarly, elevated serum calcitonin levels can lead to the early detection of thyroid medullary carcinoma. Hormones diagnostic for nonendocrine cancers are human placental lactogen and HCG. Excess production of the common alpha subunit of gonadotropins and thyrotropins occurs in approx 5% of lung or gastrointestinal cancers and up to 50% of pancreatic islet cell cancers. In addition to cancer detection, hormone markers can be used to localize cancers and to monitor responses to therapy. (7 Refs)

27. T3 IN THE SUPPRESSIVE TREATMENT OF PATIENTS TREATED BY 131I FOR THYROID CANCER: DOSES AND SERUM LEVELS (MEETING ABSTRACT).

Busnardo B, Girelli ME, Zanatta GP, Bui F, Nacamulli D
No affiliation given
Eur J Nucl Med; 6:24 1981

Suppressive therapy with thyroid hormone plays an important role in the management of differentiated thyroid cancer. This therapy is performed not only to correct the hypothyroidism after the thyroidectomy, but particularly to totally suppress pituitary secretion of thyroid stimulating hormone (TSH), thus avoiding any stimulating effect that TSH may have on tumor growth. We use triiodothyronine (T3) which is the only synthetic product available in Italy. T3 is given three x a day, at the minimum daily dose that inhibits TSH response to thyrotropin releasing hormone (TRH). In a group of 122 patients, 37 follicular and 85 papillary who had undergone total thyroidectomy and 131I therapy, the minimum TSH suppressive doses varied from 0.79 to 1.5 ug/kg/day showing a normal distribution. Serum T3 levels were measured at hourly intervals from 8 am to 11 pm in ten hospitalized patients. Mean serum level was 153 +/-43 ng/100 ml at 8 am, before the first, dose of T3, rising to 264 +/-90 ng/ml 4 hr after T3. Similar peaks were observed after each dose, slightly decreasing in the intervals. From 9 am till 11 pm the max variation of mean T3 levels was 30: The mean serum level of T3 decreased during the night, but TSH suppression remained unchanged. In fact, TSH response to TRH was completely inhibited both at 8 am, before T3, and at 4 pm. T3 in the minimum suppressive dose did not cause important side effects: nervousness 10%, insomnia 8% tachicardia 8% wt less 6%. The data showed that T3 is a safe and effective suppressive treatment in patients with thyroid cancer. (no Refs)

28. THYROGLOBULIN LEVELS IN SERA OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA. LONGITUDINAL AND CROSS-SECTIONAL STUDIES (MEETING ABSTRACT).

Schatz H, Schroder O, Grebe S
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Acta Endocrinol [Suppl]; 96(240):14 1981

For evaluating the clinical significance of thyroglobulin (TG) measurements in sera of patients with differentiated thyroid carcinoma, longitudinal and cross-sectional studies were performed. A double-antibody radioimmunoassay was used for determination of TG. Serum was taken after withdrawal of thyroxine prior to each I-131 therapy. In all sera, TG antibodies were also determined using a radio-immunoassay (CIS). Whole-body iodine scans were performed after each I-131 therapy. In 15 thyroidectomized patients TG was detectable in the circulating blood. Nine of these patients showed iodine uptake in the neck region. Positive trunk scans were registered in another group, and the highest TG levels of the whole study were measured in this sub-group. In 4 of the 6 cases, TG decreased during the past 2 yr with each I-131 therapy. These changes in TG levels were not always reflected in the scans. In another 15 patients, TG was undetectable at all times of measurement. Whereas both the neck and trunk scans were negative too in 4 patients, positive neck scans were found in 10. In 3 of the 33 patients, TG antibodies were detected so that the numerical results of the TG assay cannot be interpreted. On the other hand, no appearance of TG antibodies was observed in 30 TG-antibody negative patients during the 2 yr. Ten days after I-131 therapy, TG levels were mostly considerably higher than immediately before therapy. TG can be regarded as a tumor marker in cases of differentiated thyroid carcinoma following thyroidectomy. However, its determination can certainly not replace iodine scanning although TG measurement appears to be superior to scanning in some respect: Changes in tumor mass may be sometimes better reflected in TG levels than in conventional iodine scans. A combined application of iodine scanning and TG radioimmunoassay is thus advisable in the follow-up of patients thyroidectomized for differentiated thyroid carcinoma. (no Refs)

29. TIME COURSE STUDIES OF PLASMA THYROGLOBULIN (TG) IN METASTATIC DIFFERENTIATED THYROID CARCINOMA (MEETING ABSTRACT).

Hufner M, Kimmig B
Medizinische Poliklinik und Strahlenklinik, Heidelberg, W. Germany
Acta Endocrinol [Suppl]; 96(240):13 1981

In this study we report on the time course of plasma Tg in patients with proven metastases; in particular, plasma Tg was correlated to the presence or absence of endogenous thyroid stimulating hormone (TSH) stimulation; furthermore in selected cases Tg was correlated to the accumulated dose of radiation in the metastases during 131 I therapy. Plasma Tg was measured by a specific radioimmunoassay. Fifteen patients were followed by repeated Tg determinations for 12-22 mo. Blood samples were drawn either during suppression therapy with 0.3 mm thyroxin or after hormone withdrawal before 131 I therapy or diagnostic whole body scan. In 5 patients with scintigraphically positive metastases despite several 131 I therapies, the uptake of the radiation dose into the metastases during 131 I therapy was measured by a newly developed method using a g-camera with a pinhole collimator. Endogenous TSH stimulation seems to have a striking effect by increasing plasma Tg in some patients whereas producing no significant increase in others. Dosis uptake measurements in 5 patients who showed an unchanged scintigraphic appearance of the metastases despite several 131 I therapies revealed that in all cases no therapeutic dose was accumulated. A low Tg level dose not exclude metastases in a totally thyroidectomized patient. In metastatic thyroid carcinoma Tg levels do not generally increase during endogenous TSH stimulation; even under this condition Tg can be negative despite the presence of metastatic tissue. There seems to be no significant correlation between uptake of the radiation dose into the metastases and the Tg plasma concentration; this is exemplified by patients with scintigraphically negative metastases and elevated Tg. (2 Refs)

30. THYROID FUNCTION AFTER RADIOTHERAPY AND LARYNGECTOMY FOR CARCINOMA OF THE LARYNX.

Palmer BV, Gaggar N, Shaw HJ
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Head Neck Surg; 4(1):13-15 1981

Thyroid function of 37 patients who had received external telecobalt irradiation, total laryngectomy, and ipsilateral hemithyroidectomy is reported. Thyroid function was assessed by total levels of thyroxine (T4) and thyroid stimulating hormone (TSH) in serum. Results showed 11 patients had T4 levels less than 60 nanomole/liter (nmol/l); 4 of these showed clinical symptoms of hypothyroidism. Fifteen asymptomatic patients had T4 levels of 60-90 nmol/l; 11 had T4 levels of 90-160 nmol/l. Fourteen of 32 patients had raised TSH levels, seven of these with T4 levels less than 60 nmol/l and five with T4 levels of 60-90 nmol/l. Typical progression included subnormal T4 levels (less than 60 nano m/l) associated with raised TSH level 6 wk after surgery, and increased T4 (60-90 nmol/l) after 3 mo. Histology of the thyroid gland was normal in all 37 patients. Results suggest that thyroid gland function is depressed in a significant number of patients who have undergone external irradiation, total laryngectomy, and partial thyroidectomy. Possible causes include damage to the blood supply of remaining thyroid tissue and the effect of radiotherapy on the ability of thyroid tissue to respond to raised TSH levels. Preservation of the vasculature of the contralateral thyroid lobe, proper postoperative assessment of thyroid function, and T4 replacement are advised. (9 Refs)

31. RELATIONSHIP AMONG CIRCULATING LEVELS OF THYROID HORMONES, TSH AND TBG AFTER THYROIDECTOMY (MEETING ABSTRACT).

Iervasi G, Nicolini A, Zucchelli GC, Del Chicca MG, Bianchi R, Spisni R, Carpi A
No affiliation given
Eur J Nucl Med; 6:86 1981

Serum concentrates of T4, T3, thyroid stimulating hormone (TSH) and thyroixine-binding globulin (TBG), were measured in 6 patients submitted to thyroidectomy for differentiated thyroid cancer. Measurements were performed before surgery and at the following postoperative times: 5-10-20-30 hr, 2-3-4-5-6-8-12-15-16-18-20-24-28-30 days. Mean T4 serum levels (7 ug/dl) uniformly decreased till the value of 2.5 ug/dl. TSH serum concentrations (mean value 3.6 uU/ml) maintained constant values for a period varying in the patients from 2 to 5 days thereafter they increased till the mean value of 36.2 uU/ml. Mean TBG value (18 ug/ml) increased till the value of 27.3 ug/ml. Mean T3 levels (1.4 ng/ml) rapidly decreased in the first day, successively they reduced on in 4 patients while they increased reaching values similar to the preoperative ones in 2 patients. 131I whole body scan showed in all patients at the 30th postoperative day areas of uptake in the neck. In each patient TSH and TBG serum levels are inversely correlated with the correspondent T4 values (p 0.01 in each case). These data suggest that decrease of circulating T4 plays more of a major role than T3 to stimulate TSH secretion and it is likely responsible for the increase of circulating TBG after thyroidectomy. (no Refs)

32. HYPOTHYROIDISM FOLLOWING TREATMENT FOR HEAD AND NECK CANCER.

Vrabec DP, Heffron TJ
Dept. Otolaryngology, Geisinger Medical Center, Danville, PA, 17822
Ann Otol Rhinol Laryngol; 90(5,part1):449-453 1981

One hundred ninety-six head and neck patients were studied to determine the effects of radiation therapy and surgery on thyroid function. Serum thyroid-stimulating hormone (TSH) levels were obtained as a screening test for primary hypothyroidism. Elevated TSH levels were found in 57 of the 196 patients (29.1%). The highest incidence of abnormal TSH values (66%) occurred in the group treated with combination radiation therapy and surgery, including partial thyroidectomy. TSH levels rose early in the posttreatment period with 60% of the abnormal values occurring within the first 3 posttreatment yr. Posttreatment thyroid dysfunction was twice as common in women (48.6%) as in men (25.4). When serum thyroxine levels by radioimmunoassay (T4RIA) were correlated with the elevated serum TSH levels, a similar pattern was seen with 65% of the patients in Group 3 having a decreased T4RIA level indicating overt hypothyroidism. Pretreatment levels of thyroid function including thyroid antibody studies should be established for all patients. Serial TSH levels should be done every 3 mo during the first 3 posttreatment yr and semiannually thereafter as long as the patient will return for follow-up care. All patients treated with combination radiation therapy and surgery who develop elevated TSH levels should be treated with thyroid replacement therapy. Patients receiving radiation therapy alone should receive replacement thyroid therapy if they develop a depressed T4RIA value or a pattern of gradually increasing TSH levels. (Author abstract) (19 Refs)

33. DIAGNOSIS: THYROTOXICOSIS.

Blum M
Nuclear Endocrine Lab., New York Univ. Medical Center, New York, NY
Hosp Med; 17(10):81,82,87,88,91,96 1981

In a general discussion of thyrotoxicosis, it is noted that when thyroxine is elevated but thyrotropin (TSH) is not suppressed, the patient may have improper feedback regulation at the hypothalamic level or a tumor of the thyrotropic cells of the pituitary gland. Chorionic gonadotropin, which may be mistaken for TSH by the thyroid TSH receptor, is produced in abundance in patients with trophoblastic tumors and may cause hyperthyroidism. (no Refs)

34. EARLY RECOGNITION OF C-CELL CARCINOMA BY FAMILY SCREENING.

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Chirurgische Universitatsklinik, Robert-Koch-Str. 8, 3550 Marsburg, W. Germany
Dtsch Med Wochenschr; 106(42):1377-1380 1981

All available family members of five patients with C-cell carcinoma (medullary carcinoma of the thyroid) were tested for their basal serum-calcitonin level and after pentagastrin stimulation. In two females, aged 12 and 25 yr, from two different families, serum-calcitonin was elevated, but only after repeated tests or after pentagastrin stimulation, to definitely abnormal levels. Neither had palpable thyroid nodules, lymph-adenopathy or diarrhea. The thyroid scan was normal and there were no storage defects. But because of the family history and the elevated serum-calcitonin levels total thyroidectomy was performed in both. the specimens revealed multicentric, bilateral C-cell carcinomas. The serum-calcitonin concentration became completely normal postoperatively, so that one may justifiably speak of a curative effect of the thyroidectomy in these two instances of early diagnosis. (Author abstract) (14 Refs) (In GER)

35. CALCITONIN-LIKE IMMUNOREACTIVITY IN THE PITUITARY VASCULAR BED OF MAN.

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J Clin Endocrinol Metab; 53(5):985-989 1981

The calcitonin-like immunoreactivity (CT-like immunoreactivity) was measured in blood aspirated from the vascular bed of the anterior pituitary gland during transphenoidal surgery in 33 patients with PRL-producing microadenomas, 2 patients with Cushing's disease, and 1 patient with metastatic breast cancer with a normal pituitary gland. The mean level of CT-like immunoreactivity in the pituitary vascular bed was 2-3x higher than in peripheral blood (2.4 +-0.9 ng/ml vs 0.69 +-0.19 ng/ml), and the difference was highly significant (p less than 0.001). However, the serum ACTH, hCG, TSH, PRL, and FSH in the pituitary vascular bed was 1,000x higher than that found in the peripheral blood. The serum CT-like immunoreactivity levels in the pituitary bed in the two patients with Cushing's disease were similar to that found in other patients. Our investigations indicate (1) CT-like immunoreactivity in man is higher in the blood obtained from the pituitary vascular bed than that found in the peripheral blood; (2) the serum CT-like immunoreactivity level in the pituitary vascular bed is much less than ACTH or the other hormones secreted by the pituitary gland; (3) there is no correlation between CT-like immunoreactivity and ACTH levels. (Author abstract) (23 Refs)

36. HEALING OF OSTEOLYTIC PAGET'S BONE DISEASE DURING SYNTHETIC HUMAN CALCITONIN THE RAPY (MEETING ABSTRACT).

Whyte M, Murphy W, Haddad J, Perry M, Avioli LV
Jewish Hospital of St. Louis, St. Louis, MO
Bone Structure, Function, and Disease, March 20-21, 1981, Adelaide, South Australia. University of Adelaide 51 pp., 1981.

Paget's bone disease (PBD), characterized by progressive osteolysis followed by disorganized bone repair, may appear radiographically as discrete lytic fronts ('blade-of-grass' lesion or osteoporosis circumscriptum) during the resorptive phase. We studied the efficacy of synthetic human calcitonin (HCT) therapy by daily administration of 0.5 mg HCT (Ciba-calcin) to patients with PBD who had discrete lytic lesions. Precise, reproducible patient positioning and radiographic technique were essential for the protocol. Follow-up studies were obtained thrice yearly. Seven subjects have completed 10-45 mo of therapy. All but one responded to HCT with reductions in circulating alkaline phosphatase activity and urinary hydroxyproline. Radiographic evidence of healing was detected in 6 of the 7 patients (including one patient with osteoporosis circumscriptum). One continues to show no improvement despite one yr of therapy. Healing was detected 5 to 12 mo after HCT was initiated. Despite continued HCT therapy, reactivation and slow progression of the lytic front following healing was observed in one woman. Circulating anti-HCT antibodies were not detected in her serum. One patient decreased HCT to 0.5 mg thrice weekly and promptly showed reactivation of her 'blade-of-grass' lesion. In summary, we find that patients with PBD whose radiographs show discrete, measurable lytic fronts provide clinical investigators an excellent opportunity to meaningfully assess treatment efficacy. HCT therapy can result in arrest and healing of PBD in the osteolytic phase. (no Refs)

37. EXPERIENCES WITH SALMON CALCITONIN IN 88 PATIENTS WITH PAGET'S DISEASE OF BONE (MEETING ABSTRACT).

Grunstein HS, Clifton-Bligh P, Posen S
Endocrine Unit, Sydney Hospital, Sydney, New South Wales, Australia
Bone Structure, Function, and Disease, March 20-21, 1981, Adelaide, South Australia. University of Adelaide 51 pp., 1981.

Eighty-eight patients (45M, 43F) with radiological and scintigraphic evidence of Paget's disease were treated with salmon calcitonin. The indications for therapy were pain, neurological complications, pathological fractures, impending hip surgery and cardiac failure. The dose of calcitonin was 100 MRC units 3 x weekly or 50 MRC units daily. A few patients received both treatment schedules at different x. Almost all patients gave their own injections. Side effects included nausea, flushing, urinary frequency and diarrhea. In 16 the side effects were sufficiently severe for the patients to demand discontinuation of therapy. Four of these patients were subsequently able to tolerate porcine calcitonin. Five patients we re unable to tolerate salmon or porcine or human material. No sequential changes were observed in skeletal x-rays of bone scans except for one patient with osteogenic sarcoma. As in other series (1) urine hydroxyproline fell to approx 50% of pretreatment values during calcitonin treatment while serum alkaline phosphatase fell to approx 60% of pre-treatment values. Among 65 patients who had pain as the presenting symptom and who continued treatment for 3 mo or more, 52 reported some improvement while 13 were unimproved. Three of the unimproved patients had severe non-organic disease while in several of the other there was no obvious cause why improvement in pain should not have occurred. There was no dramatic improvement attributable solely to calcitonin among any of the patients who presented with neurological signs. At present there are no parameters which allow prediction of a response to calcitonin. (no Refs)

38. PRIMARY HYPERPARATHYROIDISM. FOUR- TO EIGHT-YEAR POSTOPERATIVE FOLLOW-UP DEMONSTRATING PERSISTENT FUNCTIONAL INSIGNIFICANCE OF MICROSCOPIC PARATHYROID HYPERPLASIA AND DECREASED AUTONOMY OF PARATHYROID HORMONE RELEASE.

Harrison TS, Duarte B, Reitz RE, Princenthal R, Seaton JF, Badder EM, Graham WP
Milton S. Hershey Medical Center, Hershey, PA, 17003
Ann Surg; 194(4):429-437 1981

Thirty-nine patients with primary hyperparathyroidism were studied 4 to 8 yr after their initial operation. In 6 patients, both the pathologist and surgeon agreed on the diagnosis of solitary adenoma; in 16 patients, the surgeon diagnosed solitary adenoma and the pathologist parathyroid hyperplasia (microscopic hyperplasia). In 16 patients, primary chief cell hyperplasia was agreed upon by the pathologist and surgeon. In the 16 patients with microscopic hyperplasia, there have been no long-term recurrences of hypercalcemia, but, in 2 patients, plasma parathyroid hormone levels are high. Parathyroid hormone - total calcium regression curves demonstrate significant preoperative correlation in solitary adenoma, p less than 0.01, and primary chief cell hyperplasia, p less than 0.05. After operation, significant correlations were not found between parathyroid hormone and total calcium. T-testing slope differences of pre- and postoperative parathyroid hormone-total calcium regression curves demonstrates a significant (p less than 0.01) shift to the right of the microscopic hyperplasia patients after operation, moving them to a broader range of total calcium per picogram parathyroid hormone. We conclude that (1) in primary hyperparathyroidism, positive regulation of total calcium by autonomously released parathyroid hormone exists in patients with solitary adenoma and primary chief cell hyperplasia; (2) autonomously functioning parathyroid tissue has been removed by operation for solitary adenoma with coexistent microscopic parathyroid hyperplasia. In thi s 4-to 8-yr follow-up period, it is clear that microscopic parathyroid hyperplasia is not associated with recurrent hypercalcemia. Two functionally distinct forms of parathyroid suppression are suggested; positively regulated microscopic hyperplasia and negatively regulated pathologically suppressed glands. (Author abstract) (14 Refs)

39. BIOCHEMICAL PARAMETERS IN HEAD AND NECK CANCER PATIENTS WITH HYPERCALCEMIA (MEETING ABSTRACT).

Angel MF, Stewart A, Pensak ML, Pillsbury HR, Sasaki CT
No affiliation given
Otolaryngol Head Neck Surg; 89(5,section2):198 1981

Hypercalcemia associated with head and neck malignancy is a common occurrence; its causes are multiple. Eight hypercalcemic patients with head and neck malignancy were studied. Nephrogenous cyclic AMP, tubular phosphorus threshold, fasting calcium excretion, plasma 1,25 dihydroxyvitamin D, and immunoreactive parathyroid hormone were measured. Excessive dietary calcium administration was the cause of hypercalcemia in two patients. Six patients demonstrated humorally mediated hypercalcemia. These patients were similar to patients with primary hyperparathyroidism in that both had elevated nephrogenous cyclic AMP excretion and reduced proximal tubular phosphorus reabsorption. They differed from patients with primary hyperparathyroidism by having normal levels of immunoreactive parathyroid hormone, sharply increased fasting calcium excretion, and strikingly reduced mean plasma levels of 1,25 dihydroxyvitamin D. These data strongly suggest that the humoral factor responsible for hypercalcemia in patients with head and neck cancer is not parathyroid hormone, but a parathyroid-like hormone with unique biochemical actions. (no Refs)

40. PLASMA VASOACTIVE INTESTINAL POLYPEPTIDE AND OTHER REGULATORY PEPTIDES IN CHILDREN WITH NEUROGENIC TUMOURS.

Tiedemann K, Long RG, Pritchard J, Bloom SR
(c/o Pritchard) Dept. Haematology and Oncology, Inst. Child Health and Hosp. Substitute for Sick Children, Great Ormond St., London WC1N 3JH, England
Eur J Pediatr; 137(2):147-150 1981

In consecutively diagnosed children with neurogenic tumors but no overt symptoms of vasoactive intestinal peptide (VIP) hypersecretion, VIP levels, changes in plasma VIP with tumor therapy, and other gastrointestinal regulatory peptide secretion by these tumors were examined. Four groups of children were studied prospectively: six children with newly diagnosed, untreated neurogenic tumors (Group A), 15 with previously diagnosed neurogenic tumors at various stages of treatment (Group B), 10 children with other tumors studied prior to treatment (Group C), and 12 otherwise normal children admitted for minor surgery (Group D). Of the six patients in Group A , three, including a child with intermittent diarrhea, had plasma VIP levels greater than 20 picomole/liter (pmol/l), with a mean of 25.8 +-11.5 p mol/l for the group. The latter value was not significantly different from the VIP levels of the 15 Group B children (11.1 +-1.25 pmol/l). Mean plasma VIP was significantly greater (p less than 0.05) than in Group C (mean 6.3 +-1.2 pmol/l) and Group D (mean 6.9 +-1.5 pmol/l). No significant differences were apparent between the groups in plasma levels of pancreatic polypeptide, gastrin, or pancreatic glucagon. The results suggested that plasma VIP may be useful as a diagnostic marker for childhood neurogenic tumors. (21 Refs)

41. THE INFLUENCE OF DIFFERENT DIETS AND SMOKING ON THE CLINICAL CHEMICAL DIAGNOSIS OF PHEOCHROMOCYTOMA, NEUROBLASTOMA, AND CARCINOID SYNDROME.

Heinemann G, Schievelbein H, Eberhagen D, Rahlfs V
Deutsches Herzzentrum Munchen, des Freistaates Bayern, Institut fur Klinische Chemie, Lothstr. 11, D-8000 Munchen 2, W. Germany
Klin Wochenschr; 59(20):1165-1173 1981

The interference of various foodstuffs on methods to determine epinephrine (E), norepinephrine (NE), vanillylmandelic acid (VMA), metanephrines (MN), homovanillic acid (HVA), and 5-hydroxyindole acetic acid (5-HIA) in the 24 hr urine for diagnosis of pheochromocytoma and carcinoid syndrome, respectively, was investigated. The foodstuffs included were: tea, coffee, almonds, pineapples, cheese, walnuts, vanilla pudding, bananas, tomatoes, and chocolate. Further, the interference of cigarette smoking on the determination of E, NE, VMA, and MN was also investigated. Walnuts caused a rather high elevation of 5-HIA in the urine. After eating bananas elevated excretion of E, NE, VMA, MN, and 5-HIA was observed. Small increases of the MN values were noticed after coffee and pineapples. Smoking of 20-30 cigarettes/day had no influence on the variables measured. If the methods described are used, thus, only bananas and walnuts have to be restricted some days before and during urine sampling, but not coffee and pineapples if consumed in the usual small quantities. There is no reason to insist on diet restriction except for bananas and walnuts. (Author abstract) (68 Refs) (In GER)

42. INDICES OF THE KININ SYSTEM IN CERTAIN DISEASES OF ABDOMINAL ORGANS.

Babalich AK, Fesenko VP
Dept. General Surgery, Crimean Medical Inst., Simferopol, USSR
Klin Khir; (8):24-26 1981

The state of the kinin system was studied in 107 patients (67 men, 40 women; 19-74 yr old) with various diseases of the abdominal organs (63/107 had cancer of the stomach). Preoperatively, the stomach cancer patients had increased levels of kininogen, bradykinin, and kininase. The most pronounced changes in the kinin system were observed in the patients with far advanced cancer. Postoperatively, the patients with Stages II-III disease showed decreases in the kininogen level. (5 Refs) (In RUS)

EFFECTS ON NORMAL AND NEOPLASTIC CELLS AND TISSUES

43. INHIBITION OF PROSTATE TUMOR GROWTH IN TWO RAT MODELS BY CHRONIC ADMINISTRATION OF D-TRP6 ANALOGUE OF LUTEINIZING HORMONE-RELEASING HORMONE.

Redding TW, Schally AV
Endocrine and Polypeptide Lab., Veterans Admin. Medical Center, New Orleans, LA, 70146
Proc Natl Acad Sci USA; 78(10):6509-6512 1981

We have investigated the effect of the D-Trp6 analogue of luteinizing hormone-releasing hormone (LH-RH), a superactive analogue of LH-RH, on the growth of two different models of prostate tumors in rats. Chronic administration of D-Trp(6)-LH-RH in a dose of 25 ug/day for 14-21 days significantly inhibited the growth of the chemically induced squamous cell carcinoma 11095 in Fisher 344 male rats. The wt of the ventral prostate and testes were also significantly reduced by treatment with this analogue. After 21 days of treatment, the animals no longer showed increases in serum luteinizing hormone and follicle-stimulating hormone levels in response to D-Trp(6)-LH-RH. Treatment of male Copenhagen F-1 rats bearing the Dunning 3327 prostate adenocarcinoma with 25 ug of D-Trp(6)-LH-RH per day for 42 days decreased the wt of both the ventral prostate and testes but had no effect on the wt of the anterior pituitary gland. The percentage increase in tumor vol was decreased to one-third and the actual tumor wt was decreased by 58% compared to untreated controls. The tumor doubling time was more than 4x longer in rats receiving D-Trp(6)-LH-RH than in controls. Serum levels of luteinizing hormone and follicle-stimulating hormone were significantly decreased in rats receiving this analogue. In both Fisher 344 and Copenhagen F-1 rats, serum prolactin and testosterone levels were significantly decreased after treatment with D-Trp(6)-LH-RH, whereas progesterone levels were increased. (Author abstract) (34 Refs)

44. ASSOCIATION OF A 68,000-DALTON PROTEIN WITH ADRENOCORTICOTROPIN-SENSITIVE ADENYLATE CYCLASE ACTIVITY IN Y1 ADRENOCORTICAL TUMOR CELLS.

Watt VM, Schimmer BP
Banting and Best Dept. Medical Res., Univ. Toronto, Toronto, Ontario M5G 1L6, Canada
J Biol Chem; 256(21):11365-11371 1981

This report explores the biochemical basis for clonal variation in adrenocorticotropin (ACTH)-sensitive adenylate cyclase activity in the Y1 mouse adrenocortical tumor cell line. We demonstrate that the level of a specific protein, designated p68, is significantly correlated with the ability of adrenocorticotropin to stimulate adenylate cyclase activity among Y1 subclones ($p = 0.004$; $r = 0.65$). p68 was characterized by its mol wt in sodium dodecyl sulfate polyacrylamide gels ($Mr = 68{,}000$) and by its isoelectric point as determined by two-dimensional gel electrophoresis ($pI = 7.2$). On two-dimensional gels, the protein migrated as a major spot with satellite spots 0.1 pH unit on either side. Homogenates and plasma membrane fractions from clones highly responsive to ACTH had large amounts of p68. In homogenates from highly responsive clones, p68 represented 10 to 12% of the total protein. Homogenates and plasma membrane fractions from clones insensitive to ACTH were deficient in p68. In homogenates from the insensitive clones Y6 and OS3, p68 represented less than or equal to 0.8% of the total protein. A somatic cell hybrid, formed by fusion of these two ACTH-insensitive clones recovered ACTH-sensitive adenylate cyclase activity and concomitantly expressed appreciable levels of p68. It is suggested that p68 may regulate the transfer of information from the occupied ACTH receptor to the catalytic subunit of adenylate cyclase. (Author abstract) (28 Refs)

45. SEROTONERGIC INFLUENCES IN CANCER ANOREXIA (MEETING ABSTRACT).

Chance WT, Von Meyenfeldt M, Fischer JE
Department of Surgery, University of Cincinnati Medical Center, Cincinnati, OH
Gastroenterology; 80(5,part2):1122 1981

Since increased brain serotonin (5-HT) activity has been associated with reduced eating, the role of 5-HT in cancer anorexia was investigated. To provide a more general demonstration of the role of 5-HT in cancer anorexia, biochemical correlates of anorexia were investigated in 8 adult male Fisher rats injected (sc) with 2 x 10(6) methylcholanthrene (MCA)-induced sarcoma cells. Saline-injected control rats were divided into freely-feeding and pair-fed groups. Food intake was significantly decreased in the tumor bearing rats (TB) by day 23 post injection, with all rats being sacrificed on day 33. Plasma free tryptophan (Trp) was elevated and albumin was decreased in the TB group. Brain tryptophan Trp, 5-HT, 5-hydroxyindol-acetic acid (5-HIAA) were also increased. Significant negative correlations were observed between food intake, tumor size and brain 5-HIAA. In a second experiment, 24 ga cannulae were implanted into the paraventricular hypothalamus of 12 TB and 12 control Fisher rats. By 35 days post-injection, ad lib feeding of the TB rats was 20% less than controls. The eating response to the intrahypothalamic (iht) injection of 24 nmol of norepinephrine (NE) in TB rats was significantly less (33%) than in controls on days 36 and 38. The influence of 5-HT in suppressing NE-induced eating was tested on days 40 and 42 by assessing the response to NE following iht pretreatment with the 5-HT antagonist, methysergide. NE-induced eating was significantly increased in both TB (31%) and control (25%) groups following the injection of methysergide. These data demonstrate that increased CNS 5-HT activity is a general phenomenon associated with anorexia and suggest this increase in CNS 5-HT may suppress NE neurons in the PVH that mediate feeding. (no Refs)

46. INCREASED BRAIN SEROTONIN ACTIVITY PARALLELS CANCER ANOREXIA (MEETING ABSTRACT).

von Meyenfeldt M, Chance WT, Fischer JE
Department of Surgery, University of Cincinnati Medical Center, Cincinnati, OH
Gastroenterology; 80(5,part2):1231 1981

Since increased brain serotonin (5-HT) activity has been associated with reduced eating, the role of this neurotransmitter in mediating cancer anorexia was investigated. The following experiments were conducted to (1) investigate the correlation of changes in brain 5-HT activity with the development of anorexia and (2) study the regional distribution of these CNS changes in tumor bearing (TB) rats. Ninety-six female SD rats (80 g) were divided into three groups: pair-fed (PF) n equals 32, freely-feeding (FF) n equals 32, and TB n equals 32. The TB rats were injected with 5 x 10(4) W 256 carcinosarcoma cells, while control rats received saline. Since this model of anorexia yields decreased eating six days after tumor transplant and spontaneous death by day 10, equal numbers of subjects were sacrificed from each group on days 3, 5, 7 and 9 for biochemical analysis. On day five, plasma free tryptophan (Trp), brain Trp, 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) were significantly elevated in TB rats as compared to FF controls, and continued to increase to yield significance between TB and both control groups by day seven. TB rats exhibited elevated Trp in the diencephalon, mesencephalon, hypothalamus, cortex, corpus striatum and cerebellum. 5-HT was increased in the diencephalon and cerebellum, while 5-HIAA was elevated in the diencephalon, pons-medulla, cortex, hippocampus and cerebellum of TB rats. These results provide additional support for the role of 5-HT in mediating cancer anorexia by demonstrating changes in the indole precursor, transmitter and metabolite within the diencephalic area of the brain just prior to clinically notable anorexia. (no Refs)

47. EFFECT OF SEROTONIN ON METHYLATION OF CHROMATIN PROTEINS IN RADIATION INJURY.

Blium IaB, Babeniuk IuD, Tsudzevich BA, Kucherenko NE
T. G. Shevchenko State Univ., Kiev, USSR
Ukr Biokhim Zh; 53(5):84-89 1981

The radioprotective effect of serotonin (ST) was studied in random-bred albino rats. ST administration (20 mg/kg, ip) 15 min prior to whole-body x-irradiation was found to modify the methylation of chromatin proteins in the liver and in the thymus. (19 Refs) (In RUS)

48. THE ROLE OF THYROID HORMONE IN RADIATION AND CHEMICALLY INDUCED ONCOGENESIS (MEETING ABSTRACT).

Borek C, Guernsey DL, Ong A
Department of Radiology, Columbia University, College of Physicians and Surgeons, New York, NY, 10032
In Vitro; 17(3):203 1981

Neoplastic transformation in vitro by x-rays and chemical carcinogens has established the direct oncogenic potential of radiation and chemicals in mammalian cells. Little is known whether hormones, normally present in mammalian serum, can affect this response. Using short-term cultures of diploid hamster embryo cells, and the heteroploid mouse cell line C3H 10T1/2 we studied the effect of triiodothyronine (T3) on transformation. We have found that in both cell types the removal of thyroid hormone from serum-supplemented culture medium (using AG1-X10 resin) inhibits radiation and chemically induced transformation while having no effect on cellular growth rate or survival. When T3 alone is added to thyroid-depleted medium at 10(-7) M, transformation frequency induced by radiation is expressed at a similar frequency as in the presence of culture medium supplemented with untreated serum. We find that exposing the cells to T3 ranging from 10(-11) M to 10(-7) M results in radiation transformation which is dose dependent. Thyroid hormone is essential for the induction and/or expression of x-ray-induced transformations. Recent findings using Benzo-a-pyrene instead of x-rays as the oncogenic agent, indicate that in the absence of T3 there is no transformation and that T3 is required for the induction and/or expression of neoplastic transformation by the chemical carcinogen. (no Refs)

49. CONTROL FACTORS FOR KERATINIZATION OF HUMAN BRONCHOGENIC EPIDERMOID CARCINOMA CELLS (MEETING ABSTRACT).

Miyazaki K, Masui H, Sato G
Department of Biology, University of California San Diego, La Jolla, CA
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

In the present study, control of the keratinization by hormones and other substances was investigated using primary-cultures of human bronchogenic epidermoid carcinoma cells derived from transplantable tumors grown in nude mice. A serum-free culture medium consisting of a basal nutrient mixture supplemented with selenium, ***insulin, triiodothyronine*** (T3), and glucagon was formulated. This medium supported growth of epidermoid carcinoma cells better than serum-supplemented medium. When epidermoid carcinoma cells were cultivated in serum-free medium without T3 for longer than three wk, they underwent a marked morphological change producing stratified cell clusters. That this morphological change represents keratinization of epidermoid carcinoma cells was evidenced by the following: 1) stratified cells were stained red with Rhodamine B; 2) stratified cells were insoluble in 1% sodium dodecyl sulfate (SDS), but dissolved in a mixture of 1% SDS and 1% 2-mercaptoethanol; 3) antiserum against human stratum corneum keratin cross-reacted with extract from stratified cells. The addition of T3 or retinoic acid to serum-free medium at concentrations higher than 10(-10) M strongly inhibited the keratinization. The keratinization of epidermoid carcinoma cells was also inhibited almost completely in culture medium containin g newborn calf or other kinds of serum at concentrations higher than 0.3%. The anti-keratinization activity of serum was removed by extraction with acetone but not by dialysis. The addition of retinoic acid to the acetone-treated serum restored the anti-keratinization activity to control serum levels. (no Refs)

50. HORMONES AND FACTORS WHICH STIMULATE GROWTH OF A RAT ISLET TUMOR CELL LINE IN SERUM-FREE MEDIUM (MEETING ABSTRACT).

Fong H, Chick WL, Sato GH
Department of Biology, University of California, San Diego, La Jolla, CA
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

A number of hormones and factors were found to stimulate growth of cultured rat islet tumor cells, the RIN-r cell line. A serum-free supplemented medium for RIN-r cells was formulated consisting of a 1:1 mixture of Hams's F12 and DME media with the addition of insulin, transferrin, triiodothyronine, prolactin, growth hormone and an extract of proteose peptone (medium IM). The growth rate of RIN-r cells in this medium is as great as in 10% serum-supplemented medium and up to ten population doublings occur over a period of 20 days. Insulin is a very effective mitogen for RIN-r cells with an effect at concentrations as low as 30 ng/ml. In addition, the insulin-like somatomedin, multiplication stimulating activity (MSA), is a growth factor at 50 ng/ml. It was found that RIN-r cells proliferate and continue to produce immunoreactive insulin in a hormonally and nutritionally defined medium, derived from medium IM, in which insulin is replaced with MSA and proteose peptone is omitted. Variations of this medium may prove useful in studies on the growth and function of normal islets in long term primary culture. (no Refs)

51. GROWTH RESPONSE TO INSULIN AND MSA IN MOUSE MELANOMA CELLS AND FIBROBLAST X MELANOMA HYBRIDS (MEETING ABSTRACT).

Coppock DL, Straus DS
Biomedical Sciences Division and Biology Department, University of California, Riverside, CA, 92521
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Further studies have been performed with the PG19 mouse melanoma cells and one of the insulin-responsive hybrid clones to investigate the biochemical basis for the complementation for the insulin response observed in the hybrids. In hormone-supplemented serum-free medium, the hybrid cells but not the melanoma cells require insulin for optimal growth. Thus the growth response to insulin of the two cell types in serum-free medium is consistant with the growth response observed in confluent growth-arrested cultures. Like insulin, the insulin-like growth factor multiplication stimulating activity (MSA) stimulates 3H-thymidine incorporation in the fibroblast x melanoma hybrid cells but not in the parental melanoma cells. The PG19 melanoma cells and the hybrid cells have approx the same number of high and low affinity insulin receptors, and both cell types also have high affinity MSA receptors. Interestingly, insulin strongly stimulates 3H-leucine incorporation in the hybrid cells over a broad concentration range, while in the melanoma cells it does not have a significant effect in most experiments and has a marginally significant effect in others. Two possible explanations for these results are that the melanoma cells have a postreceptor block in the growth response to insulin and MSA, or that processes controlled by insulin are never growth-limiting in these cells, whereas such processes can be made growth-limiting in the hybrids. One class of variants appears to arrest more completely in medium with low serum than the parental hybrid cells, and to have a more stringent requirement for serum-derived growth factors for exit from G1. (1 Ref)

52. A GENETIC APPROACH TO STUDIES OF INSULIN ACTION IN CLOUDMAN S91 MELANOMA CELLS (MEETING ABSTRACT).

Murray M, Fleischmann R, Pawelek J
Department of Dermatology, Yale University School of Medicine, New Haven, CT, 06510
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Wild-type Cloudman S91 mouse melanoma cells have prolonged generation times when insulin is added to culture medium containing either horse or fetal calf sera. However, in the defined, serum-free medium of Mather and Sato the cells are stimulated to proliferate by insulin. In both cases the effects are mediated through specific high affinity insulin receptors. The effects of insulin on proliferation are dissociable from those on amino acid transport and glycogen synthesis. We isolated a number of mutants which are resistant to the inhibitory effects of insulin in serum-containing medium, and have identified three distinct phenotypes: insulin inhibited (wild-type), insulin resistant, and insulin dependent. In addition, 'revertants' of the insulin dependent line were selected which no longer require insulin for proliferation. Each revertant line expressed the insulin-resistant phenotype. The insulin dependent line was about 15 x more sensitive than the wild-type to the effects of insulin, and is, to our knowledge, the only line described which is stimulated to proliferate by concentrations of insulin in the 0.1-1.0 nM range. In addition, the insulin dependent line exhibited insulin-mediated protein phosphorylation patterns which differed from those seen in wild-type cells. We have produced hybrids between cells from each of the above four phenotypic categories. By testing the effects of insulin on proliferation of hybrid clones, we were able to determine that insulin inhibition is dominant over both insulin dependence and insulin resistance, and that insulin dependence is dominant over insulin resistance. The results indicate that a detailed genetic analysis of the regulation of insulin action in these cells is feasible. The Cloudman melanoma line represents the first system available for such studies. (1 Ref)

53. ANTILEUKEMIC EFFECT OF SOMATOSTATIN (MEETING ABSTRACT).

Pavelic K, Gabrilovac J, Bozikov V, Pavelic J, Petek M, Boranic M
Department of Biological Medicine, Rudjer Boskovic Institute, 41001 Zagreb, Yugoslavia
Exp Hematol; 9(Suppl9):184 1981

Since one of the effects of somatostatin is suppression of insulin secretion, we decided to test whether somatostatin would cause retardation of growth of an insulin-dependent tumor. The experiments were carried out in RF mice with a transplantable myeloid leukemia. This tumor grows more slowly in mice with alloxan-induced diabetes than in normal mice, hence it is an insulin-dependent tumor. Daily injections of somatostatin (0.5 to 50 ug/mouse/day in 3 portions, ip) retarded the tumor growth. The effect was dose-dependent. Somatostatin decreased the level of immunoreactive insulin in the plasma of mice with leukemia, and treatment with insulin abrogated the antileukemic effect of somatostatin. Hence we attribute retarded growth of this leukemia under the treatment with somatostatin to decreased secretion of insulin. Another possible mechanism of antileukemic effect of somatostatin might be suppression of secretion of the growth hormome, which is, like insulin, needed for growth of some human and experimental leukemias. Thus, somatostatin might have abated progression of this murine leukemia through endocrine mechanisms - either via insulin, or via the growth hormone. (3 Refs)

54. PANCREATIC CANCER GROWTH STIMULATION BY CAERULEIN AND SECRETIN (MEETING ABSTRACT).

Townsend CM, Franklin RB, Watson LC, Glass EJ, Thompson JC
Department of Surgery, University of Texas Medical Branch, Galveston, TX, 77550
Newsletter Natl Pancreas Cancer Project; VI(2):59 1981

Caerulein (C), alone, or in combination with secretin (S) produces hyperplasia of the normal rat pancreas. The effects of these hormones on pancreatic ductal cancer (as well as normal hamster pancreas) are unknown. The purpose of this study was to determine whether pancreatic trophic hormones stimulate growth of pancreatic ductal cancer in Syrian golden hamsters. We used a tissue culture cell line of hamster pancreatic ductal cancer developed in our laboratory. Groups of 8 male hamsters were inoculated with 5x10(5) cells into the left cheek pouches. After 7 days of tumor growth, treatment was begun with 0.15 M NaCl for controls (CON), and with either C (15 ug/kg/day) or S (75 ug/kg/day), or a combination of C + S. Divided daily doses were given by ip injection (0.5 ml) every 8 hr for 15 or 20 days. At sacrifice, tumors (T) and normal pancreas (P) were excised, weighed, and the DNA content determined. Trophic hormones for normal hamster pancreas appear to stimulate growth of pancreatic cancer. To our knowledge, this is the first demonstrated endocrine stimulation of pancreatic ductal carcinoma. (no Refs)

55. THE ROLE OF ERYTHROPOIETIN IN ERYTHROID COLONY FORMATION FROM RAUSCHER LEUKEMIA VIRUS-INFECTED MICE.

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Exp Hematol; 9(9):938-944 1981

Recent work has led to conflicting results regarding the in vitro control of erythropoiesis in mice infected with Rauscher Leukemia Virus (RLV). Some reports claimed that marrow or splenic erythropoiesis from RLV-infected mice were independent of exogenously added erythropoietin (Ep), while other reports supported the view that erythroid stem cells (CFUE) from RLV-infected mice required Ep for erythroid differentiation and proliferation. Results reported here demonstrate that CFUE cultured from RLV-inoculated mice are dependent upon Ep for erythroid differentiation. Furthermore, RLV-infected mice which had received transfusions to suppress the endogenous production of Ep not only had a reduction in spleen wt and reticulocyte percentage, but also reduced numbers of CFUE and BFUE. (Author abstract) (20 Refs)

EFFECTS OF ENDOGENOUS AND EXOGENOUS AGENTS ON NON-STEROID HORMONE ACTIVITY

56. EFFECTS OF MEGESTROL ACETATE ON GROWTH AND SECRETION OF A PITUITARY TUMOR.

Lamberts SW, Janssens EN, Bons EG, Zuiderwijk JM, Uitterlinden P, De Jong FH

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Eur J Cancer Clin Oncol; 17(8):925-931 1981

The effect of the administration of the 6-methylated progestagen megestrol acetate on the growth of the estrogen-induced transplantable PRL/ACTH-secreting rat pituitary tumor 7315a was investigated. A significant inhibition of tumor growth was observed only during the last wk of a 4 wk period of drug administration (6 mg/kg). Administration of megestrol acetate suppressed the total content and the ability to release PRL, ACTH and LH of the pituitary gland of tumor bearing rats. Further, a significant suppression of the anterior pituitary, ovarian and uterine wt was observed in the megestrol acetate treated animals. Megestrol acetate did not exert a direct effect on PRL, ACTH and LH secretion by normal rat pituitary glands incubated in vitro. We conclude that megestrol acetate exerts in the model used a suppressive effect on PRL, ACTH and LH release and led to a diminution of the pituitary content of these hormones, whil e it has also anti-estrogenic and anti-androgenic properties. The effects of the drug help further explain its beneficial effects in metastatic breast, endometrial, renal and prostatic cancer in man. (Author abstract) (30 Refs)

57. A MET-ENKEPHALIN ANALOG INHIBITS ADRENOCORTICOTROPIN SECRETION BY CULTURED PITUITARY CELLS FROM A PATIENT WITH NELSON'S SYNDROME.

Lamberts SW, Oosterom R, Verleun T, Bons EG, Uitterlinden P

Dept. Medicine III, Univ. Hosp. 'Dijkzgt' 40, Dr. Molewaterplein, 3015 GD Rotterdam, The Netherlands

J Clin Endocrinol Metab; 53(5):1084-1086 1981

ACTH secretion by cultured nonenzymatically dispersed pituitary tumor cells from a patient with Nelson's syndrome was studied. Hormone release was suppressed by 74 +-6% by the addition of 1 uM of the met-enkephalin analog FK 33824, while naloxone (1 uM) stimulated ACTH release by 70 +-5%. Somatostatin, dexamethasone, bromocriptine and cyproheptadine in a concentration of 1 uM each inhibited ACTH release by 25 +-2%, 35 +-2%, 52 +-2%, and 61 +-4%, respectively, while lysine vasopressin (0.1 uM) and dibutyryl cAMP (5 mM) stimulated ACTH release by 112 +-8% and 220 +-4%, respectively. In conclusion, it was shown that the stimuli mentioned above directly affect ACTH secretion by the pituitary tumor cells. The inhibitory action of the met-enkephalin analog and the stimulatory action of naloxone on ACTH secretion make the presence of opiate receptors on this type of tumor likely. (Author abstract) (15 Refs)

58. CHARACTERIZATION OF CALCITONIN- AND ADRENOCORTICOTROPIN-PRODUCING HUMAN CLONED CELL LINES.

Dermody WC, Rosen MA, Ananthaswamy R, Levy AG, Hixson CV, Aldenderfer PH, Nelson-Rees WA, Marangos PJ, Swanson EC

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J Clin Endocrinol Metab; 53(5):970-977 1981

We have developed three human cloned cell lines that produce immunoreactive human calcitonin (ihCT) and ACTH (iACTH) as well as exhibit characteristics of cultured neural cells. Clones HMS-41/I,-78/2, and-98/2 were developed from cell lines HeLa AV3, MBA 9812 (bronchogenic carcinoma), and SW 267 (pheochromocytoma), respectively. Karyological analysis of both the parent and the cloned cell lines confirmed the identity of HeLa AV3 and MBA 9812. When grown in serum-free media designed for culturing neural cells, the patterns of production for both ihCT and iACTH varied among the clones. The multiple patterns of hormone production suggest that the mechanisms involved in the biosynthesis, processing, and secretion of these hormones differ among the clones. The clones contain neuron-specific enolase and the putative neurotransmitters beta-alanine and gamma-amino butyric acid, and they respond to cAMP analogs by differentiating, as noted by the extension of neurites (except the HeLa-derived HMS-41/I). The iACTH extracted from cells a nd synthetic ACTH exhibited equivalent profiles upon isoelectric focusing. The forms of ihCT noted in cell extracts were similar to those observed in extracts of human tumor tissue. Our rabbit antiserum to hCT failed to detect ihCT in those cell extracts prepared for ACTH determination or in extracts of rat pituitaries, but it did detect CT in rat thyroids by both RIA and immunofluorescent procedures. We concluded that our antisera to hCT do not detect the precursor form of ACTH. The availability of these cloned cell lines provides model systems for examining the production of these peptide hormones and the concomitant expression of neural and endocrine characteristics. (Author abstract) (56 Refs)

59. 3,5,3'-TRIIODOTHYRONINE(T3) AND 3,3'5',-TRIIODOTHYRONINE (REVERSE T3;RT3) SYNTHESIS IN TUMOR-BEARING ANIMALS (MEETING ABSTRACT).

Ong M, Malkin DG, Malkin A

Department of Clinical Biochemistry, Sunnybrook Medical Centre, Toronto, Canada

Oncodev Biol Med; AbstractsBook,1:52 1981

Since the synthesis of rT3 appears to be a characteristic feature of fetal ontogeny, we undertook to determine whether a reversion from T3 to rT3 synthesis would take place in experimental animal tumors and, in addition, whether hepatic and renal deiodination of T4 would show a similar reversion in these tumor-bearing animals. We chose as animal models the R3230AC mammary tumor grown in Fischer 344 rats and two variants of the Morris 5123 hepatoma, the 1-1 and 81-B, grown in Buffalo rats. Tumor, hepatic and renal tissues were analyzed for 5-and 5'-deiodinase activity using standard techniques. The following results were obtained: (1) in the Fischer 344 rats, the mammary tumor was found to contain both 5-and 5'-deiodinase activities (normal lactating mammary glands contain no detectable enzyme activity), (2) compared to normal controls, hepatic and renal T3 synthesis increased significantly while rT3 synthesis remained unaltered in the mammary tumor-bearing rats, (3) in the hepatoma-bearing rats, the hepatomas contained 5- and 5'-deiodinase activity comparable to those present in the liver, (4) both T3 and rT3 synthesis were significantly less than normal in the liver of the hepatoma-bearing rats, (5) renal synthesis of T3 and rT3 in both normal and all tumor-bearing rats was significantly greater than hepatic synthesis of these hormones. We conclude that: (1) significant differences in the behavior of 5-and 5'-deiodinase occur in different tumor models, (2) there is no evidence of retro-differentiation of 5-deiodinase activity either within the tumor or at remote sites in these particular animal models. (no Refs)

60. ONCOGENIC TRANSFORMATION AND THE REDUCTIONS OF INSULIN SECRETION AND PROLIFERATIVE CALCIUM DEPENDENCE DURING REPEATED PASSAGE OF PANCREATIC ISLET CELLS IN VITRO.

Whitfield JF, Boynton AL, Healy GM, Sun AM

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Cancer Lett; 14(2):159-168 1981

Changes in calcium-dependent ability to secrete insulin and proliferative calcium-dependence of fetal bovine pancreatic islet cells during passage through successive generations were analyzed. Although the insulin content of fetal pancreas did not change appreciably between passage 3 and 12, insulin secretion fell to non-detectable levels over this period. Proliferation of islet cells could be stopped or greatly lowered by reducing the calcium concentration from 1.8 to 0.02 milliM. However, as with insulin secretion, this sensitivity to extracellular calcium deprivation declined and eventually vanished as the cells passed through successive generations and their proliferative capacity increased. Reductions of insulin secretion and proliferative calcium dependence were accompanied by oncogenic transformation. (29 Refs)

61. GLUCOSE TOLERANCE AND HORMONAL CHANGES IN RATS BEARING A TRANSPLANTABLE SARCOMA.

Singh J, Grigor MR, Thompson MP
(c/o Thompson) Dept. Biochemistry, Univ. Otago, P.O. Box 56 Dunedin, New Zealand
Int J Biochem; 13(10):1095-1100 1981

Changes in insulin and glucagon metabolism were studied in sarcoma-bearing NZBW rats. Basal insulin and glucagon levels were measured to determine the pattern of their interrelationship during various stages of tumor growth. Iv glucose tolerance tests were carried out in the rats to determine if the ability of the host to metabolize glucose and return the blood glucose concentration to normal was impaired. The response of pancreatic B cells was also studied by measuring insulin levels during the glucose tolerance tests and after tolbutamide administration. (25 Refs)

62. DIFFERENTIAL SECRETION OF OPIOID PEPTIDES AND CATECHOLAMINES FROM CULTURED CELLS OF A HUMAN PHEOCHROMOCYTOMA TUMOR.

Wilson SP, Slepetis R, Chang KJ, Kirshner N, Viveros OH
Wellcome Res. Lab., Res. Triangle Park, NC, 27709
Life Sci; 29(22):2257-2264 1981

Dissociated cells from a human pheochromocytoma tumor were maintained in culture, and the secretion of opioid peptides (OP), endogenous catecholamines (CA) and preloaded [3H]norepinephrine from these cells was examined. Nicotine, veratridine, barium or Ionomycin stimulated the secretion of OP, endogenous CA and 3H from the pheochromocytoma cells. In general, the different secretagogues were more potent in releasing OP than endogenous CA; 3H secretion was intermediate. Secretion of OP was more sensitive to stimulation by the calcium ionophore Ionomycin and by veratridine than was CA secretion. Nicotine-evoked OP secretion was more sensitive to extracellular calcium concentration than was secretion of CA or 3H. In contrast, bovine adrenal chromaffin cells show no such differential secretion of OP and CA in response to Ionomycin stimulation or to nicotine stimulation under conditions of varying extracellular calcium concentration. The results show that human pheochromocytomas secrete OP as well as CA and that there may be heterogeneous storage pools of CA and OP in cultured pheochromocytoma cells. (Author abstract) (17 Refs)

RECEPTOR/ BINDING SITES

63. RELATIONSHIP BETWEEN BIOLOGICAL RESPONSIVENESS TO PHORBOL ESTERS AND RECEPTOR LEVELS IN GH4C1 RAT PITUITARY CELLS.

Jaken S, Tashijian AH, Blumberg PM
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Cancer Res; 41(12):4956-4960 1981

During a 24-hr incubation of GH4C1 cells with phorbol esters or thyrotropin-releasing hormone, there is a decrease in the number of phorbol ester receptors (down-modulation). The purpose of this study was to investigate whether this decrease in receptor number attenuated cellular responsiveness to subsequent challenge with phorbol esters. Accordingly, cellular sensitivity to a phorbol ester-mediated biological response, namely the decrease in binding of epidermal growth factor, was compared in control and down-modulated cells. This phorbol ester-mediated event is closely associated with phorbol ester receptor occupancy, and it is therefore an effect for which altered dose-response characteristics correlating with alterations in the number of phorbol ester receptors could be anticipated. In fact, during a 48-hr exposure to phorbol esters, GH4C1 cells become refractory to the effect on epidermal growth factor binding. This time course is similar to that for the loss of phorbol ester receptors. However, when cells are down modulated by pretreatment with phorbol ester or thyrotropin-releasing hormone and then (re)challenged with phorbol ester, no differences in dose-response characteristics were observed between control and down-modulated cells. We therefore conclude that phorbol ester receptor down-modulation does not affect cellular responsiveness to phorbol esters, at least when decreased epidermal growth factor binding is used as the marker for the phorbol ester-mediated event. (Author abstract) (21 Refs)

64. SPECIFIC BINDING OF 125I-INSULIN IN PLASMA MEMBRANES OF FAT CELLS IN PATIENTS WITH PHEOCHROMOCYTOMA.

Bezdrobnyi IuV, Evdokimova NIu, Efimov AS, Komissarenko IV, Demchenko NP

Diabetes Dept., Inst. Endocrinology and Metabolism, Kiev, USSR

Probl Endokrinol (Mosk); 27(5):38-42 1981

The insulin receptors of fat cell membranes were studied in seven pheochromocytoma patients. The membranes were isolated from surgery specimens of paranephric or mesenteric fat and were incubated with labeled and nonlabeled insulin. The pheochromocytoma patients showed a significant decrease in specific binding of the 125I-insulin. The decrease was due to reduction of insulin-binding sites and decreased affinity for insulin. The changes in the state of the insulin receptors were associated with an increased level of catecholamines. (14 Refs) (In RUS)

65. INSULIN RECEPTOR FUNCTION AND REGULATION IN ERYTHROBLASTIC LEUKEMIC CELLS.

Galbraith RA

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Diss Abstr Int [B]; 42(4):1333-B 1981

The erythroblastic leukemic (EBL) cell is a chemically induced tumor cell, passaged in vivo in rat pups, which has been used as a model cell for normal erythroblasts. This cell was used to test the hypothesis that the insulin receptors on RBC are vestigial, being left over from their earlier nucleated stages of development when they expressed insulin receptors which were coupled to biological response. Studies showed the EBL cells did have specific insulin receptors but displayed marked insulin degradation. Using either bacitracin or high doses of bovine serum albumin to inhibit such degradation to acceptable levels, competitive insulin binding assays were performed. Subsequent Scatchard analysis showed that EBL cells have 22,000 receptors per cell whereas RBC have 60. Receptor affinity showed less marked differences. EBL cell insulin receptors were also coupled to biological responses. The demonstration of insulin receptors coupled to biological response in EBL cells supports the concept that RBC insulin receptors may be vestigial. Insulin-induced down-regulation in EBL cells and the electron microscopic demonstration of insulin internalization support the concept that EBL cell receptors are regulated by the circulating insulin concentration. (no Refs)

66. DESENSITIZATION TO GONADOTROPINS IN CULTURED LEYDIG TUMOR CELLS INVOLVES LOSS OF GONADOTROPIN RECEPTORS AND DECREASED CAPACITY FOR STEROIDOGENESIS.

Freeman DA, Ascoli M
(c/o Ascoli) Div. Endocrinology, Dept. Medicine, Dept. Biochemistry, Vanderbilt Medical Sch., Nashville, TN, 37232
Proc Natl Acad Sci USA; 78(10):6309-6313 1981

The ability of human choriogonadotropin (hCG) to regulate its receptors and target cell responses has been studied in a clonal strain of cultured Leydig tumor cells (MA-10). Exposure of the MA-10 cells to hCG results in decrease in hCG binding activity which is dependent on time and the concentration of hCG. This decrease is due to a change in the number of receptors rather than in the affinity of the receptors, and it is accompanied by a corresponding reduction in the ability of hCG to stimulate steroidogenesis. Exposure of the MA-10 cells to hCG also resulted in a reduction of the steroidogenic responses to cholera toxin and 8-Br-cyclic-AMP. The hCG-induced loss of steroidogenic responses to these stimuli seems to be due to the stimulation of steroidogenesis rather than to the decrease in hCG receptors because it also can be induced when steroidogenesis is stimulated with cholera toxin or 8-Br-AMP under conditions such that the number of hCG receptors is not reduced. (Author abstract) (21 Refs)

67. PRESENCE OF ECTOPIC BETA-ADRENERGIC RECEPTORS ON HUMAN ADRENOCORTICAL CORTISOL-PRODUCING ADENOMAS.

Hirata Y, Uchihashi M, Sueoka S, Matsukura S, Fujita T
Third Div., Dept. Medicine, Kobe Univ. Sch. Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650, Japan
J Clin Endocrinol Metab; 53(5):953-957 1981

A direct binding study of radioligand [3H]dihydroalprenolol (DHA), a potent beta-adrenergic antagonist, was performed on the particulate fractions of four adrenocortical adenomas (3 cortisol-producing adenomas and 1 aldosterone-producing adenoma) and normal adrenal tissues. The effect of epinephrine on cortisol production was also evaluated in vitro from the cultured tumor cells from one cortisol-producing adenoma. Saturable binding of [3H]DHA to the tumor membranes was observed in two of three cortisol-producing adenomas, but not in the aldosterone-producing adenoma or in normal adrenal tissues. Scatchard analysis of equilibrium binding of [3H]DHA revealed a single class of binding sites on the tumor membranes; the apparent dissociation constant (Kd) was 1 nM in each, and the numbers of binding sites were 108 and 45 fmol/mg protein, respectively. Competition by adrenergic agents with [3H]DHA for binding sites on the membranes from one cortisol-producing adenoma revealed that (+-)propranolol, a beta-adrenergic antagonist, was about 350-fold more potent than phentolamine, an alpha-adrenergic antagonist, suggesting the beta-adrenergic nature of receptor sites. In addition, stereospecificity was demonstrated by about 1,000-fold greater affinity of (-)alprenolol than to (+)alprenolol, both of which are stereoisomers of the beta-adrenergic antagonist. Furthermore, production of cortisol from the cultured tumor cells prepared from the same adenoma was significantly stimulated by epinephrine in addition to ACTH. These data indicate that ectopic beta-adrenergic receptor sites are present in some human adrenocortical tumors which may be functionally related to the activation of adenylate cyclase by catecholamines other than ACTH in those tumors, as previously demonstrated. The mechanism by which such altered cellular membrane characteristics occur in association with neoplastic alteration of the endocrine tissues remains unanswered. (Author abstract) (20 Refs)

OTHER RELATED STUDIES

68. THYMIN AND CELL MEDIATED IMMUNITY.

Jin Y
Dept. Biology, Nanjing Univ., Nanjing, People's Republic of China
Shengli Kexue Jinzhan; 12(2):126-131 1981

Research on the physiological role of thymus hormones in cell-mediated immunity is reviewed. The hormones act on immature lymphocytes of the thymus and peripheral blood to transform them int o the mature T-lymphocytes that take part in cell-mediated immunity of the organism. They consist of a group of polypeptides and proteins; more than 20 have been isolated and named, including thymosin, thymopoietin I, thymopoitin II, thymin, and serum thymic factor. They have been used in China as immunologic regulators combined with chemotherapy in treating immunologic deficiency syndromes, autoimmune disease, and small cell carcinoma of the lung. Results so far have been very promising. The analysis of thymus hormones, the roles of cyclic nucleotides (cAMP and cGMP), and the role of aging in relation to the immune system are described. (48 Refs) (In CHI)

69. RECENT DEVELOPMENTS IN RESEARCH ON GUT HORMONES.

Wu Y, Jiang S, Jiang S

Dept. GI Diseases, Shanghai Second Medical Coll., Shanghai, People's Republic of China

Zhonghua Xiaohua Zazhi; 1(1):58-63 1981

The secretion and biological functions of numerous gastrointestinal hormones in normal and diseased states are described. The hormones include gastrins, vasoactive intestinal peptide (VIP), pancreatic polypeptide, cholecystokinin (CCK), gastric inhibitory polypeptide (GIP), somatostatin (SRIH), bombesin, neurotensin, endorphins, and encephalin. Some of the hormones are common to the gastroenteropancreatic endocrine system and the nervous system. The significance and role of the hormones in diseases of the digestive system are discussed. (26 Refs) (In CHI)

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HORMONES IN CANCER-RELATED BIOLOGY

Non-Steroid Hormones

SERIES CB24 No. 82/04

APRIL, 1982

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CHARACTERIZATION OF NON-STEROID HORMONES IN EXPERIMENTAL AND IN VITRO SYSTEMS

1. PRACTICAL APPLICATIONS OF IMMUNOCYTOCHEMISTRY TO THE PHARMACOLOGY AND TOXICOLOGY OF THE ENDOCRINE SYSTEM.

El Etreby MF
Res. Lab., Schering AG, Mullerstr. 170/178, D-1000 Berlin 65, W. Germany
Histochem J; 13(5):821-837 1981

Practical applications of immunocytochemistry in the investigation of endocrine glands and genital organs in pharmacologic and toxicologic studies are discussed. Using the immunoperoxi-

HE 20.3173/2:

dase technique and specific antisera, selective immunocytochemical staining can be localized in the various cell types found in the pituitary gland. Most hormones of the pars distalis and pars intermedia can be f ound in corresponding specific cell population. Diffuse hyperplasia and hypertrophy of either growth hormone or prolactin producing cells or both have been demonstrated immunocytochemically in the pituitarys of old dogs and estrogen and/or progestagen-treated Beagles. Using specific antisera and not labelled antibody peroxidase-antiperoxidase method, somatostatin was localized in a large population of immunoreactive neurons in the periventricular areas of the preoperative region and anterior hypothalmus of dogs. Using the immunoperoxidase technique and a specific antiserum against uteroglobulin, it has also been possible to localize specific staining in certain secretory cells of the rabbit endometrium in the preimplantation phase and after progesterone stimulation. Immunoreactive endogenous prolactin and growth hormone were detected in hyperplastic and neoplastic lesions of the dog prostate and mammary gland using the basic immunocytochemical procedure. Immunospecific prolactin and growth hormone staining was localized in different mammary tumors of the dog. Certain structural components of the mammary tumors, notably the myoepithelial elements and ductal epithelium, revealed predominant growth hormone-positive staining. These findings may explain the importance of growth hormone rather than prolactin in the pathogenesis of spontaneous and progestagen-related mammary tumors in the dog. (42 Refs)

CLINICAL, DIAGNOSTIC AND PROGNOSTIC STUDIES

2. A PROSPECTIVE STUDY OF PLASMA PROLACTIN LEVELS AND SUBSEQUENT RISK OF BREAST CANCER.

Kwa HG, Cleton F, Wang DY, Bulbrook RD, Bulstrode JC, Hayward JL, Millis RR, Cuzick J
Antoni van Leeuwenhoek-Huis, Netherlands Cancer Inst., Plesmanlaan 121, 10066CX Amsterdam, The Netherlands
Int J Cancer; 28(6):673-676 1981

Plasma prolactin was measured in 2,572 premenopausal, 628 menopausal, and 1,666 peri- and postmenopausal women who were apparently healthy. Breast cancer was subsequently diagnosed in 47 of these women at a median time of 5 years after blood collection (pre-cancer cases). Prolactin levels in premenopausal cases increased significantly with age whereas this was not found in matched controls. The perimenopausal cases were characterized by extreme variability in prolactin levels. In post-menopausal women who developed breast cancer, the prolactin levels were significantly elevated, being at or above the 70th percentile for the controls. In this group the results are consistent with prolactin acting as a late-stage tumor promoter. (Author abstract) (18 Refs)

3. HYPERPROLACTINEMIA IN MAN: CLINICAL INDICATIONS AND THERAPY.

Eversmann T, Eichinger R, Fahlbusch R, Rjosk HK, Von Werder K (c/o von Werder), Medizinische Klinik Innenstadt, Ziemssenstrasse 1, D-800 Munchen 2, W. Germany
Schweiz Med Wochenschr; 111(47):1782-1789 1981

Fifty-seven male patients with hyperprolactinemia have been investigated. Macroadenomas were found in 49 patients of whom 24 had received pituitary surgery before elevated PRL levels were discovered. In eight patients radiology of the pituitary fossa revealed either evidence of microadenoma or a completely normal sella turcica. Prolactin levels ranged from 582 to 498,000 uU/ml. All patients with macroprolactinomas, including those who had undergone previous surgery, had PRL levels above 5,000 uU/ml. Disturbances of libido and sexual potency were prevalent in the majority of patients, less frequently accompanied by gynecomastia and galactorrhea. However, visual disturbances were the reason for the first visit to the doctor in the majority of patients. Pituitary surgery led to improvement of visual field defects, though prolactin levels were never normalized. Postoperative radiotherapy had no significant influence on PRL levels. In contrast, bromocriptine therapy led, in the majority of patients not only to improvement of hypogonadal symptoms but also to normalization of PRL levels. (Author abstract) (28 Refs) (In GER)

4. COMPARISON OF THE RESPONSES IN THE NOMIFENSINE TEST WITH HYPERPROLACTINEMIA DUE TO PROLACTIN-SECRETING PITUITARY TUMORS AND NONPROLACTIN-SECRETING HYPOTHALAMIC TUMORS.

Kamoi K, Tchuchida I, Sato H, Tanaka R, Ishiguro T, Kaneko K, Iwasaki Y, Shibata A
Dept. Internal Medicine, Nagaoka Red Cross Hosp., Nagaoka 940, Japan
J Clin Endocrinol Metab; 53(6):1285-1287 1981

It has recently been proposed that nomifensine (Nom) administration discriminates those patients with PRL-secreting pituitary tumors from those who have hyperprolactinemia due to other causes. In the present study, this test was performed on 12 presumed functional hyperprolactinemic subjects, 9 patients with surgically proved PRL-secreting pituitary adenoma (6 microadenoma and 3 macroadenoma), and 7 patients with surgically proved non-PRL-secreting hypothalamic tumors (3 craniopharyngioma, 3 suprasellar germinoma, and 1 suprasellar ependymoma). The Nom test suppressed the plasma PRL level to below 60% of the basal level in all 12 women with presumed functional hyperprolactinemia, but did not alter plasma PRL levels in the patients with PRL-secreting pituitary adenoma or hypothalamic tumor. This evidence confirms that the test is, at least in part, able to discriminate those individuals with PRL-secreting pituitary adenoma from those without, regardless of the size of the tumor. However, the test is not capable of distinguishing between hyperprolactinemia due to PRL-secreting pituitary tumors and that due to non-PRL-secreting hypothalamic tumors. A lack of response to Nom is not necessarily due to the presence of a PRL-secreting tumor, and may be related to dysfunction of the hypothalamic-pituitary system. (Author abstract) (14 Refs)

5. EFFECT OF CIMETIDINE ON SERUM PROLACTIN IN NORMAL WOMEN AND PATIENTS WITH HYPERPROLACTINEMIA.

Carlson HE, Chang RJ, Meyer NV, Lu KH, Judd HL
Endocrinology Section, Veterans Administration Wadsworth Medical Center, Wilshire and Sawtelle Boulevards, Los Angeles, CA, 90073
Clin Endocrinol (Oxf); 15(5):491-498 1981

The effects of cimetidine (CMT) on pituitary hormone release were studied in eight normal women (22-41 yr old) and 20 patients (7 men, 13 women; 20-61 yr old) with non-puerperal hyperprolactinemia (6 prolactinoma, 2 acromegaly, 2 hypothalamic cysts, and 10 idiopathic hyperprolactinemia). Thirteen post-partum women were also studied as a model of physiological hyperprolactinemia. Following iv CMT injection, serum prolactin (PRL) in normal women rose significantly from a mean baseline value of 7.7 +-2.3 nanog/ml to a peak of 33.7 +-4.5 nanog/ml (p less than 0.005). Serum growth hormone, thyrotrophin, luteinizing hormone, and follicle stimulating hormone were not significantly altered after CMT administration. Six of eight patients with pituitary tumors showed a lower PRL response to iv CMT than normal women. In 7/8 tumor patients, the absolute PRL response to thyrotrophin releasing hormone (TRH) was greater than the response to CMT (p less than 0.05). In only 4/8 patients, did the absolute PRL less than response to TRH fall below the range seen in normal women. When expressed as a percentage increment over baseline, the PRL responses to both CMT and TRH were markedly blunted when compared to normal women, with no overlap between the tumor and normal groups. The percentage increments in PRL were greater following TRH than CMT in 7/8 tumor subjects (p less than 0.05). Approx half of idiopathic hyperprolactinemia patients showed lower PRL responses to both CMT and TRH than normal women; in 7/10 subjects, the absolute response to TRH was greater than the response to CMT (p less than 0.05). The two patients with hypothalamic lesions showed responses generally similar to those of the previous two groups. Post-partum subjects tended to have enhanced PRL response to provocative tests. The results indicated that dynamic testing of PRL secretion with CMT is no more useful than TRH in distinguishing tumorous from non-tumorous hyperprolactinemia. (24 Refs)

6. BENSERAZIDE, A STIMULATOR OF PROLACTIN RELEASE: A NEW TEST IN THE DIAGNOSIS OF PITUITARY PROLACTIN-SECRETING TUMOURS.

Pontiroli AE, Falsetti L, Voltolini AM, Alberetto M, Pellicciotta G, De Pasqua A, Girardi AM, Pozza G
Ospedale San Raffaele, 20132 Milano, Italy
Acta Endocrinol (Copenh); 98(3):326-332 1981

Benserazide, an extra-cerebral inhibitor of dopa-decarboxylase, elicits prolactin (Prl) release in normal subjects when administered po. The aims of this study were to characterize the effect of benserazide on Prl release and to evaluate benserazide as a diagnostic tool in hyperprolactinemic patients. In normal subjects, the effect of 50 mg benserazide is reduced to a greater extent by 500 mg than by 200 mg l-dopa, and is nullified by dopamine (DA, 50 mg iv in 180 min), which also decreases fasting plasma Prl levels. Doses of 25, 50 and 150 mg benserazide elicit Prl responses which are slightly and progressively but not significantly higher; a second dose of 50 mg, administered 150 min later, is without effect on Prl release, while TRH (200 ug iv) elicits a further Prl peak. Since it is known that consecutive doses of TRH yield progressively lower Prl responses while 5-hydroxytryptophan (the precursor of serotonin) further increases Prl release in response to benserazide, we hypothesize that, in an area involving both the hypothalamus and the pituitary gland, anti-DA drugs (benserazide), TRH, and serotonin stimulate Prl release by interacting with different kinds of receptors. When administered to hyperprolactinemic patients, benserazide stimulated Prl release in puerperal women and in patients with functional hyperprolactinemias, but was totally ineffective in patients with pituitary adenomas, whatever the fasting plasma Prl levels. on two patients with a normal sellar tomography in whom benserazide induced no Prl release, a second tomography or computerized axial tomography of the brain, performed respectively 3 and 6 mo later, revealed a pituitary microadenoma. These results suggest that benserazide may be a valuable diagnostic tool in the differential diagnosis of hyperprolactinemia. (Author abstract) (19 Refs)

7. SURGICAL TREATMENT OF PITUITARY ADENOMAS: EARLY OR LATE DIAGNOSIS AND TREATMENT.

Nesbakken R, Reinlie S, Norman N
Dept. Neurosurgery, Ulleval Hosp., Oslo, Norway
J Oslo City Hosp; 31(10):117-127 1981

Fifty patients with pituitary adenomas, who were diagnosed without the help of the ophthalmologist, were treated by transsphenoidal microsurgery according to the methods of Cushing, Guiot, and Hardy. All were evaluated by an endocrinologist and all had x-ray findings consistent with a pituitary lesion, and all but one had positive endocrinological findings. Immediate endocrine changes (prolactin [PRL], growth hormone, thyroid stimulating hormone) during and after tumor excision were followed by sequential blood sampling, with later samples analyzed by radioimmunoassay. There was one diagnostic failure, and one serious operative complication, purulent meningitis. Early hormone assays indicate radical surgery if serum PRL is less than 500 ug/liter (except in one patient in whom surgery was terminated because orientation was lost). (7 Refs)

8. LONG-TERM EFFECTS OF ENDOCRINE TREATMENT ON SERUM PITUITARY HORMONES IN ADVANCED PROSTATIC CARCINOMA PATIENTS.

Lukkarinen O, Hammond GL, Kontturi M, Vihko R
Dept. Surgery, Univ. Oulu, Oulu 22, Finland
Scand J Urol Nephrol; 15(3):207-211 1981

Peripheral serum concentrations of FSH, LH, prolactin and ACTH were measured in 22 patients with advanced prostatic carcinoma treated by castration, polyestradiol phosphate (Estradurin(R)) administration and a combination of castration and Estradurin(R) administration during the first 12 months of treatment. Estradurin(R) treatment alone (80 mg im once a month) did not result in any significant changes in the circulating concentrations of FSH, LH and prolactin. Therefore, the clear-cut inhibition of testicular steroidogenesis observed under this kind of treatment does not appear to be due to an inhibition of pituitary gonadotropin secretion, and is most likely due to a direct estrogen effect on Leydig cells. Castration led to grossly elevated serum FSH and LH levels. In this group, serum FSH remained at a high level, whereas LH was close to pretreatment levels 9 months after castration, suggesting differences in pituitary capacity to secrete FSH and LH under these conditions. Concentrations of circulating FSH, and to a lesser extent LH, in the combination treatment group were between those found in the castration and estrogen-only treatment groups, suggesting that the secretion of both gonadotropins can be suppressed by estrogen. No changes in serum prolactin and ACTH concentrations were seen in the three treatment groups. (Author abstract) (21 Refs)

9. PITUITARY ADRENAL AXIS DURING TRANSSPHENOIDAL PITUITARY ADENOMECTOMY.

Sodoyez JC, Stevenaert A, Demey-Ponsart E, Sulon J, Dehavay P
Dept. Internal Medicine and Neurosurgery, Univ. Liege, Liege B-4020, Belgium
Ann Endocrinol (Paris); 42(3):280-281 1981

ACTH secretion during surgical removal of pituitary adenomas was compared in patients with prolactin (PRL) and GH secreting tumors to patients with Cushing's disease. ACTH blood levels were determined by specific radioimmunoassay. ACTH levels peaked during pneumoencephalography and/or during transsphenoidal approach and at the end of anesthesia in patients with GH or PRL secreting tumors. ACTH levels in patients with Cushing's disease peaked during microdissection of the tumor. Apparently GH and RPL secreting tumors did not markedly alter the response to stress of the cerebrohypothalamo-pituitary adrenal axis, while the preoperative surge of ACTH in patients with Cushing's disease can be tentatively attributed to mechanical disruption of adenomatous cells. (2 Refs)

10. CLINICAL AND ENDOCRINE SPECTRUM IN PATIENTS WITH THE 45,X/46,XY KARYOTYPE.

Kofman S, Perez-Palacios G, Medina M, Escobar N, Garcia M, Ruz L, Mutchinick O, Lisker R

Servicio de Genetica, Unidad de Patologia, Escuela de Medicina, Hospital General de la S.S.A, U.N.A.M., Mexico 7, D.F., Mexico

Hum Genet; 58(4):373-376 1981

The correlation between gonadal morphology, endocrine dynamics, phenotypic expression, and cytogenetics was studied in five unrelated patients (3 male, 2 female; 6-20 yr old) with 45,X/46,XY karyotypes. The external phenotypic characteristics of the patients are described. Three of the patients developed gonadoblastomas, one in the ectopic testis (Patient C), one from a streak gonad (Patient A), and one from ovarian stroma (Patient B). The X-chromatin was negative in all patients. Karyotypic results are presented. Two patients (Patients C and D) showed abnormal non-fluorescent Y chromosomes. Persistently elevated serum gonadotropins were found in Patients A and B. Administration of luteinizing hormone (LH)-releasing hormone (LH-RH) induced significant increase in both LH and follicle stimulating hormone (FSH) in both patients. Serum testosterone (T) levels were extremely low and did not respond to human chorionic gonadotropin (HCG) stimulation. In Patient A, serum androstenedione was 0.45 nanog/ml and showed significant increase following HCG stimulation. Elevated LH and FSH levels with normal LH-RH response were found in Patient C. Circulating T levels were within normal lower values. HCG administration induced subnormal although significant increase in serum T. Low LH and FSH levels with normal pituitary LH-RH responsiveness were found in Patient D. Serum T levels were detectable but below normal. HCG stimulation produced a small but significant increase in serum T. Patient E had normal LH and FSH serum levels. LH-RH stimulation significantly increase LH levels. Serum T levels were extremely low with a diminished but significant response to HCG. The results show the clinical variability of patients with 45,X/46,XY karyotype. (13 Refs)

11. COMPREHENSIVE RADIONUCLIDE EXAMINATION OF THE FUNCTIONAL STATE OF THE HYPOPHYSEAL-THYROID SYSTEM IN TOXIC THYROID ADENOMAS.

Kashkadamov AV

Res. Inst. Endocrinology and Metabolism, Kiev, USSR

Med Radiol (Mosk); 26(10):40-43 1981

Functional state of the hypophyseal-thyroid system was studied in 21 patients (30-60 yr old) who had toxic thyroid adenoma. Scintigraphy with the use of 131I failed to differentiate between the patients with clinical symptoms of thyrotoxicosis and those without. Radioimmunoassay of thyroid hormones showed, however, significant increases in blood levels of thyrotropin, triiodothyronine, and thyroxine in the patients with the clinical symptoms. (17 Refs) (In RUS)

12. CYCLICAL COMBINATION CHEMOTHERAPY AND THYROID FUNCTION IN PATIENTS WITH ADVANCED HODGKIN'S DISEASE.

Sutcliffe SB, Chapman R, Wrigley PF

Dept. Radiation Oncology, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario, M4X 1K9, Canada

Med Pediatr Oncol; 9(5):439-448 1981

Clinical and biochemical assessment of thyroid function was undertaken in patien ts with Hodgkin's disease at designated points following diagnosis. At diagnosis, 2 of 20 patients had either abnormally low routine thyroid indices, or elevated thyroid stimulating hormone (TSH) levels that were not due to iodine-based investigations. Following lymphography, 76.5% of patients had TSH levels that remained elevated for a median period of 3 mo. No detectable thyroid dysfunction was induced during chemotherapy. Fifty-four patients were studied at a median time of 35 mo after chemotherapy. One euthyroid patient had a nodular goiter, and one had abnormal thyroid indices. TSH levels were elevated in 44% of patients, although the median TSH level for the group was normal. Half the patients had abnormal TRH stimulation tests. Sixty patients were studied after irradiation and chemotherapy. Four patients had clinical thyroid dysfunction, and 10% of routine thyroid indices were abnormal. TSH levels were abnormal in 80%, with a markedly elevated median level. All thyroid releasing hormone stimulation tests were abnormal. (Author abstract) (28 Refs)

13. THYROXINE AND TRIIODOTHYRONINE LEVELS IN THYROID VEIN BLOOD AND IN THYROID TISSUE OF PATIENTS WITH AUTONOMOUS ADENOMAS.

Gheri RG, Borrelli D, Cicchi P, Legnaioli M, Fabbroni S, Modigliani U, Gheri G, Serio M

(c/o Serio) Endocrinology Unit, Univ. Florence, Viale Morgagni 85, 50134 Florence, Italy

Clin Endocrinol (Oxf); 15(5):485-490 1981

Thyroxine (T4) and triiodothyronine (T3) were measured by specific radioimmunoassays in peripheral and thyroid vein blood and in nodular and extranodular thyroid tissue from 24 patients with autonomous thyroid nodules (AFTN). Thirteen patients with solitary non-functioning thyroid adenomas, who were clinically euthyroid, served as controls; samples of thyroid vein blood and normal thyroid tissue were obtained from the contralateral lobe. Hyperthyroidism was exhibited by 15 of the AFTN patients while 9 were euthyroid. Concentrations, expressed as nanomole/liter, of T4 (189 +-27.2) and T3 (7.05 +-2.03) were significantly higher in the thyroid vein blood of AFTN patients compared with controls (T4, 119 +-9.1, p less than 0.05; T3, 2.3 +-0.21, p less than 0.01). Concentrations in peripheral vein blood were similar in the two groups. Concentrations of T3 (nanomole/g wet tissue) were significantly higher in autonomously-functioning thyroid nodule tissue (10.56 +-4.12) compared to extranodular (1.9 +-0.62, p less than 0.01) and normal thyroid tissue (2.63 +-0.43, p less than 0.05). T4 levels did not differ significantly in the nodular and extranodular tissues of patients and normal thyroid. T3 concentrations in nodular tissues were higher than those in extranodular (p less than 0.01) and normal (p less than 0.05) parenchyma. There was no correlation between thyroid hormone concentrations in the inferior vein of the gland and tis sue, either in patients or in controls. T4 and T3 concentrations in thyroid and peripheral venous blood did not correlate. (11 Refs)

14. THE COMPARATIVE VALUE OF SERUM THYROGLOBULIN MEASUREMENTS AND IODINE 131 TOTAL BODY SCANS IN THE FOLLOW-UP STUDY OF PATIENTS WITH TREATED DIFFERENTIATED THYROID CANCER.

Ashcraft MW, Van Herle AJ
(c/o Van Herle) Dept. Medicine, Div. Endocrinology, UCLA Sch. Medicine, Los Angeles, CA, 90024
Am J Med; 71(5):806-814 1981

This study is an attempt to unify the evaluation of patients with well-differentiated thyroid cancer after ablative therapy. As such, serum thyroglobulin determinations on and off thyroid hormone (T4) therapy and iodine 131 total body scans were examined in 53 patient studies. No metastases were found in patients whose thyroglobulin value was undetectable (less than 1 ng/ml). Values during T4 therapy that were detectable, even as low s 4.2 ng/ml, were occasionally associated with metastases. After T4 withdrawal, thyroglobulin value and scan were obtained. Neither metastasis nor clinically detectable cancer was found in patients whose thyroglobulin value was less than 10 ng/ml while off T4. Conversely, a value greater than 10 ng/ml was often associated with documented metastases even when the scan was negative. In summary, a thyroglobulin value less than 1 ng/ml during T4 therapy or less than 10 ng/ml off T4 therapy suggests successful therapy and a routine scan could be avoided unless clinically indicated. However, a value greater than 10 ng/ml suggests the presence of metastasis despite a negative scan. Thyroglobulin determination substantially improves the management of these patients. (Author abstract) (45 Refs)

15. SYNTHETIC CALCITONIN FROM SALMON IN THERAPY OF OSTEOLYTIC METASTASES DUE TO MAMMARY CARCINOMA.

Simone C, Racanelli A
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Clin Ter; 98(3):247-267 1981

Eighty-one mammary carcinoma (MC) patients (25-68 yr old; 79 women and 2 men) with osteolytic metastases were divided in two groups with one man in each group. In the first group 41 MC patients received calcitonin and radiotherapy (15), different protocols of polychemotherapy [(14 patients) adriamycin, vincristine, 5-fluorouracil, and endoxan], and 12 patients were given hormone therapy (suppressive or additive antiestrogens or high dose progesterone derivatives). Forty patients of the second group received radiotherapy 2500-3000 rads (15), chemotherapy (15), and hormone therapy (10). Clinical, biochemical, and radiologic evaluation was performed before, and 1, 3 and 6 mo after the start of therapy. Thirty-nine patients of the first group received calcitonin 20 days/mo for 6 mo, and 2 received calcitonin for only 2 mo. The decrease of pain occurred after first mo and persisted beyond 6 mo, regardle ss of type of treatment. Radiotherapy alone had the same effect, but of shorter duration and starting later (3 mo). Calcitonin had favorable effect on hypercalcemia and hypercalciuria. Osteolytic metastatic lesions were recalcified, but after 6 mo osteolysis reappeared in the same location. Further treatment was not effective. (27 Refs) (In ITA)

16. SERUM GASTRIN LEVELS IN PATIENTS WITH PHEOCHROMOCYTOMA.

Sagara K, Oishi S, Umeda T, Sato T
Third Dept. Internal Medicine, Kumamoto Univ. Medical Sch., 1-1-1 Honsho, Kumamoto 860, Japan
Jpn J Clin Oncol; 11(2):363-366 1981

The clinical significance of serum gastrin levels was investigated in 11 pheochromocytoma patients, 26 essential hypertension patients, and 20 healthy controls. There were no significant differences in either epinephrine or norepinephrine excretion between normal controls and hypertensive patients, while pheochromocytoma patients showed abnormally high secretion of epinephrine or norepinephrine or both. Abnormally high serum gastrin levels in pheochromocytoma patients returned to normal after resection of the tumor. Epinephrine was found to affect serum gastrin levels to a greater extent than norepinephrine. High serum gastrin levels were found in patients bearing epinephrine-secreting tumors. Normal gastrin levels were observed in patients with extra-adrenal tumors. Assay of serum gastrin levels in patients about to undergo surgical resection of pheochromocytoma may aid in location of the tumor. (11 Refs)

17. THE C-PEPTIDE SUPPRESSION TEST IN NORMAL PERSONS AND INSULINOMA PATIENTS: AN ATTEMPT TO EVALUATE ITS USE IN FUNCTIONAL DIAGNOSIS.

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(c/o Kuhnau) Med. Kernklinik und Poliklinik, Univ.-Krankenhaus Eppendorf, Martinistr. 52-07-, D-2000 Hamburg 20, W. Germany
Klin Wochenschr; 59(21):1209-1215 1981

C-Peptide and insulin are secreted in equimolar amounts by the pancreatic beta cells. In certain situations where insulin itself cannot be measured, the determination of the C-peptide concentration in the serum may replace the observation of insulin concentration. Under this aspect the determination of C-peptide is performed in the C-peptide suppression test. It serves to demonstrate whether the endogenous insulin secretion is suppressible by an insulin injection or not. In this way, functional hyperinsulinism can be differentiated from autonomous tumor hyperinsulinism, the latter not being suppressible by insulin induced hypoglycemia. In regard to the reviewed literature we agree with other authors that the C-peptide suppression test yields a pathological result in 85% of insulin-producing tumors. (23 Refs) (In GER)

18. THE EFFECT OF BROMOCRIPTINE ON INSULIN SECRETION AND GLUCOSE TOLERANCE IN PATIENTS WITH ACROMEGALY.

Feek CM, Bevan JS, Taylor S, Brown NS, Baird JD
Dept. Medicine, Western General Hosp., Univ. Edinburgh, Edinburgh EH4 2XU, Scotland
Clin Endocrinol (Oxf); 15(5):473-478 1981

Twelve patients with acromegaly were treated over an av period of 12 mo (range 3-27 mo) with bromocriptine (BCR; 5 mg every 6 hr, po). BCR significantly reduced whole blood glucose, plasma insulin, and plasma growth hormone (GH) levels during a 50 g oral glucose tolerance test (OGTT). Blood samples were obtained after an overnight fast and at 30-min intervals for 2 hr after po administration of 50 g glucose. Repetition of OGTT 48 hr after withdrawal of BCR revealed a significant rise in whole blood glucose, plasma insulin, and plasma GH. BCR therapy appears to improve glucose tolerance in acromegaly by suppressing GH secretion and consequently GH-mediated antagonism of insulin. (16 Refs)

19. HYPOGLYCEMIA ASSOCIATED WITH NON-ISLET-CELL TUMOR AND INSULIN-LIKE GROWTH FACTORS. A STUDY OF THE TUMOR TYPES.

Gorden P, Hendricks CM, Kahn CR, Megyesi K, Roth J
NIH, Building 10, Room 9N222, Bethesda, MD, 20205
N Engl J Med; 305(24):1452-1455 1981

Plasma samples from 52 patients with non-islet-cell tumors associated with fasting hypoglycemia were examined. Insulin-like growth factor (ILGF) was found in 19 samples (37%) at levels greater than 150% of the normal control levels. When individual tumor types were considered, 6/7 patients with hemangiopericytoma had elevated values. Elevations of ILGF were also observed in patients with other mesenchymal tumors, hepatoma, adrenocortical carcinoma, and pheochromocytoma. Patients with lymphomas had distinctly low values of ILGF. The nature of ILGF is unknown, but it circulates bound to a high-mol wt-protein. In one patient with a hemangiopericytoma involving the liver, irradiation of the liver mass resulted in a fall in ILGF levels and a marked improvement in fasting hypoglycemia. The causes of hypoglycemia in the non-islet-cell hypoglycemia syndrome appear heterogeneous; involvement of ILGF in the syndrome seems to predominate in patients with certain tumor types. (10 Refs)

20. CEREBROSPINAL FLUID HUMAN CHORIONIC GONADOTROPIN LEVELS IN NORMAL PREGNANCY AND CHORIOCARCINOMA.

Berkowitz RS, Osathanondh R, Goldstein DP, Martin PM, Mallampati SR, Datta S
New England Trophoblastic Disease Center, Div. Gynecologic Oncology, Brigham and Women's Hosp., Boston, MA
Surg Gynecol Obstet; 153(5):687-689 1981

We measured human chorionic gonadotropin levels simultaneously in the serum and cerebrospinal fluid of 36 normal pregnant women and of 6 patients with choriocarcinoma. During normal pregnancy, human chorionic gonadotropin levels in the cerebral spinal fluid correlated well with those in the serum in both the first and third trimesters. A serum-cerebral spinal fluid human chorionic gonadotropin ratio of less than 60 has previously been reported as a sensitive diagnostic test for trophoblastic CNS involvement. However, we found this ratio to be less than 60 in one patient undergoing first trimester abortion and in one patient with nonmetastatic choriocarcinoma. Furthermore, two patients with documented trophoblastic cerebral metastases had serum-cerebral spinal fluid human chorionic gonadotropin ratios in excess of 60. Results of our study, thus, indicate that determination of a single serum-cerebral spinal fluid human chorionic gonadotropin ratio may not conclusively prove or exclude trophoblastic CNS metastases. Unless it is corroborated by other diagnostic means, a single decreased serum-cerebral spinal fluid human chorionic gonadotropin ratio is insufficient evidence to initiate multimodality treatment for presumptive CNS involvement. (Author abstract) (3 Refs)

21. THE HCG-IMMUNOASSAY FOR THE EARLY DETECTION OF CANCER.

Navarro MD, Navarro EF
No affiliation given
Acta Manila Ser A; (20):12-21 1981

The efficacy of human chorionic gonadotropin (HCG) immunoassay for early cancer detection is discussed. Sensitivity and specificity of the assay were tested in 3,446 confirmed cancer cases (the majority with cancer of the respiratory system, breast, uterus, liver, and stomach). Elevation of urinary HCG could be detected much earlier than the tumor became apparent. A postoperative HCG test could be used for recurrence detection. Disadvantages of the HCG test include difficulties in differentiating between pregnancy and tumor, failure to pinpoint the tumor site, and cross-reaction with luteinizing hormone. Continuous determination of HCG urinary level can be used to monitor the effectiveness of therapy. (14 Refs)

EFFECTS ON NORMAL AND NEOPLASTIC CELLS AND TISSUES

22. INFLUENCE OF PROLACTIN AND GROWTH HORMONE ON RAT MAMMARY TUMORS INDUCED BY N-NITROSOMETHYLUREA.

Rose DP, Noonan JJ
Div. Clinical Oncology, Wisconsin Clinical Cancer Center, Univ. Wisconsin, Madison, WI, 53792
Cancer Res; 42(1):35-38 1982

The effects of hypophysectomy and prolactin-suppressing drugs on the growth of mammary tumors induced in Sprague-Dawley rats by N-nitrosomethylurea and dimethylbenz(a)anthracene were compared. The influence of ovine prolactin and growth hormone administration on N-nitrosomethylurea-induced tumors was also studied in hypophysectomized animals. After hypophysectomy, all 13 tumors induced in 13 rats by N-nitrosomethylurea underwent regression, as did 10 of 12 induced by dimethylbenz(a)anthracene. There were no new tumors. Pergolide mesylate, a long-acting ergoline derivative, was given in a dose of 80 ug bid by sc injection for 28 days. Only 3 of 12 N-nitrosomethylurea-induced tumors regressed, while 4 became static. However, only two new tumors developed in the 12 pergolide-treated rats, compared to 11 in the 12 untreated controls. Bromocriptine mesylate, at 10x the pergolide dose, was even less effective; one of 16 tumors regressed, 2 became static, and 8 new tumors appeared in the 16 rats. In contrast, 8 of 12 dimethylbenz(a)anthracene-induced tumors regressed during pergolide therapy, 2 became static, and there was only 1 new tumor among the 12 rats. Prolactin, 1 mg bid for 7 days by sc injection, was given to another eight rats bearing 11 N-nitrosomethylurea-induced tumors, commencing 7 days after hypophysectomy. Regression of five tumors borne by four rats was reversed but resumed when treatment was stopped. Regression of five tumors in the other four animals was arrested without regrowth; the sixth became impalpable. All of these six grew rapidly when growth hormone, 2 mg bid, was administered in addition to prolactin. (Author abstract) (21 Refs)

23. CORRELATION OF CIRCULATING LEVELS OF A SERUM PROTEIN WITH TRIIODOTHYRONINE LEVELS AND HEPATOMA GROWTH.

Coetzee ML, Short J, Klein K, Ove P
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Cancer Res; 42(1):155-160 1982

In this communication, we provide evidence that proliferation of transplantable Morris hepatoma 7777 might to some extent be regulated by triiodothyronine and/or a specific serum protein, the levels of which are correlated with levels of triiodothyronine. The protein has an estimated mol wt of 80,000 and migrates as one band on polyacrylamide gel electrophoresis. In normal rats, this protein accounts for approx 1% of the total serum protein. Both the circulating levels of the serum protein and proliferation of transplanted hepatoma cells were decreased in thyroidectomized rats. Elevated levels of the serum protein and increased cell proliferation were observed when animals had 70% of their liver removed prior to transplant, were given injections of triiodothyronine, or had a 10-day-old first transplant surgically removed. Some evidence is also provided suggesting that the synthesis of the serum protein is stimulated by thyroid hormone. (Author abstract) (36 Refs)

24. MANIFESTATION AND GROWTH OF TRANSPLANTABLE OSTEOSARCOMA IN MICE: THE EFFECT OF THYMECTOMY AND THYMOSIN TREATMENT.

Carlsson SR, Stigbrand T, Boquist L, Lundgren E, Winblad B, Larsson SE
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Clin Orthop; (159):279-285 1981

The effect of thymectomy and thymosin (TS) treatment on tumor growth, structural appearance and immunity was studied in male CBA mice inoculated with tumor cell suspensions originating from the Dunn osteosarcoma. The mice were divided into five groups (Group I controls, Groups II and IV thymectomized, and Groups III and IV TS-treated) with 15-17 mice/group. In Groups I, III, and IV, the tumor frequency was 80-94%, while in Group II, a significantly higher proportion (p less than 0.001) of mice were tumor free (tumor frequency 47%). Group II also showed the lowest mean tumor wt. No obvious structural differences were found among the tumors of the different groups. However lymphocytic infiltration with a slight admixture of plasma cells was observed at the periphery of Group II tumors. In all groups, very low specific lysis was observed; only at a lymphocyte/tumor cell ratio of 300:1 was a significant difference established. Group II mice showed a higher degree of cytotoxic activity (p less than 0.01) than the rest of the groups. Normal animals not subject to tumor cell injections responded in the same apparent magnitude as Groups I, III, and IV. Even extensive immunization produced no measurable increase in lysis. Neither cytotoxic nor growth inhibiting antibodies were found in any of the sera tested. No significant correlation was seen between tumor wt and specific lysis of tumor cells, although the five animals with the highest specific lysis were tumor-free. The results indicated that CBA mice bearing this osteosarcoma did not develop cell-mediated or humoral-immune response against the tumor. (15 Refs)

25. REGULATION OF TYROSINE AMINOTRANSFERASE BY INSULIN IN CULTURED RAT HEPATOMA CELLS.

Sorimachi K, Yasumura Y
Dept. Microbiology, Dokkyo Univ. Sch. Medicine, Mibu, Tochigi 321-02, Japan
J Biochem (Tokyo); 90(4):1197-1204 1981

Tyrosine aminotransferase (TAT) activity in cultured rat hepatoma cells (R117-21B) was induced by insulin. Activity was max at 6-8 hr after incubation and then decreased. The degree of induction of TAT activity was related to insulin concentration in the range 0.005-0.5 nanog (ng)/ml. Enzyme activity reached a plateau after 6 hr incubation at concentrations greater than 0.5 ng/ml. The number of insulin binding sites (IBS) in R117-21B cells was 2.5 x 10(5)/cell. The dissociation constant of the insulin receptor system at 25 C was 3.7 nanoM. Max TAT activity occurred when only 1.9% of IBS were occupied. Each cell took up 3,900 insulin molecules. TAT activity increased after insulin was added in a fresh culture medium. Certain components of the incubated medium (IM) inhibited the reinduction of TAT activity. TAT activity was reinduced after addition of insulin-untreated fresh cells. Some cellular modulation occurred during the insulin treatment; together with components contained in the IM, the modulation inhibited reinduction of TAT activity by fresh insulin. The inhibitory effect was related to the proportion of IM to fresh medium during the induction. Unknown IM components were heat-stable and could not be extracted with ethanol or acetic acid from lyophilized IM. Insulin induces intracellular modulation in hepatoma cells; inhibitory components also contribute to regulation of TAT activity by insulin. (26 Refs)

26. METABOLIC MODIFICATION BY INSULIN ENHANCES METHOTREXATE CYTOTOXICITY IN MCF-7 HUMAN BREAST CANCER CELLS.

Alabaster O, Vonderhaar BK, Shafie SM
Dept. Medicine, George Washington Univ., Suite 625, 2150 Pennsylvania Ave., N.W., Washington, DC, 20037
Eur J Cancer Clin Oncol; 17(11):1223-1228 1981

Insulin, which activates and modifies metabolic pathways in MCF-7 human breast cancer cells, is shown to increase the cytotoxic effect of methotrexate up to 10,000-fold in vitro. This enhanced cytotoxicity is not due to an increased bound intracellular drug level, an increased growth rate or an increase in S phase cells, but may involve the modification or activation of biochemical pathways associated with cell growth, even in cells not undergoing DNA synthesis. This observation supports the hypothesis that tumor cell sensitivity to chemotherapy could be increased by using agents that can activate the biochemical or metabolic pathways that determine the cytotoxic process. (Author abstract) (13 Refs)

27. EFFECTS OF INSULIN ON CELLULAR GROWTH AND PROLIFERATION.

Straus DS
Biomedical Sciences Div., Univ. California, Riverside, CA, 92521
Life Sci; 29(21):2131-2139 1981

Insulin stimulates the growth and proliferation of a variety of cells in culture. The growth-stimulatory effects of insulin are observed in G0/G1 arrested cells limited for serum growth factors or essential nutrients, and in cells growing in hormone-supplemented serum-free media. Some, but not all, of the effects of insulin on growth require superphysiological concentrations of insulin. The action of insulin on growth is synergistic with the action of other hormones and growth factors, including FGF, PDGF, PGF2alpha, and vasopressin. This observation, as well as other observations regarding the temporal sequence of action of growth factors, suggests that different growth factors act on different intracellular biochemical events. Several hypotheses have been proposed to explain the effect of insulin on cellular proliferation, including regulation of essential metabolic processes and interaction of insulin with receptors for insulin-like growth factors. Evidence supporting these various hypotheses is reviewed. In addition to the growth-stimulatory effect of insulin observed in cell culture, a number of clinical examples suggest that insulin is an important growth-regulating hormone during fetal development. (Author abstract) (87 Refs)

28. RUTHENIUM RED-INSENSITIVE CALCIUM TRANSPORT IN ASCITES-SARCOMA 180/TG CELLS.

Bygrave FL, Anderson TA
Dept. Biochemistry, Faculty Science, Australian Natl. Univ., Canberra, A.C.T. 2600, Australia
Biochem J; 200(2):343-348 1981

Ruthenium Red-insensitive Ca++ transport in the mouse ascites sarcoma 180/TG is enriched in a 'heavy' microsomal fraction (microsomes) sedimented at 35,000 g for 20 min. The subcellular distribution of this Ca++ transport differed from that of Ruthenium Red-sensitive Ca++ transport and (Na+ + K+)-dependent ATPase activity, but was similar to that of glucose 6-phosphatase. The affinity of this transport system for 'free' Ca++ is high (Km approx 6 uM) and that for MgATP somewhat lower (Km approx 100 uM). Ca++ transport by the tumor microsomes, by contrast with that by liver microsomes, was greatly stimulated by low concentrations of Pi. Although incubation of intact ascites cells with glucagon led to an increase in intracellular cyclic AMP, no stable increase in the initial rate of Ca++ transport in the subsequently isolated 'heavy' microsomes could be detected as in similar experiments carried out previously with rat liver cells. Reconstitution experiments suggest that a deficiency exists in the tumor microsomal membrane such as an action of glucagon that is normally present in rat liver microsomes is not evoked. (Author abstract) (20 Refs)

29. VASOACTIVE INTESTINAL POLYPEPTIDE MODULATION OF LYMPHOCYTE ADENYLATE CYCLASE.

O'Dorisio MS, Hermina NS, O'Dorisio TM, Balcerzak SP
Dept. Medicine, Ohio State Univ., 410 W. 10th Ave., Columbus, OH, 43210
J Immunol; 127(6):2551-2554 1981

Vasoactive intestinal polypeptide (VIP) was found to be a potent stimulator of lymphocyte adenylate cyclase activity. VIP-induced activation of adenylate cyclase was specific for lymphocytes among peripheral blood cells; ie, VIP did not stimulate the adenylate cyclase activity of neutrophils, monocytes, or platelets. The VIP-induced activation of lymphocyte adenylate cyclase was time, temperature, and concentration dependent. VIP and the GTP analog, Gpp(NH)p, acted synergistically to stimulate lymphocyte adenylate cyclase; stimulation by VIP and PGE1 was additive; and VIP activation was antagonized by somatostatin. VIP-mediated activation of lymphocyte adenylate cyclase was observed in normal human T cells, B cells obtained from a patient with chronic lymphocytic leukemia, and a human T cell culture line. The Raji human B cell culture line did possess adenylate cyclase activity, but this activity was not stimulated by VIP. These results suggest that lymphocytes possess functional receptors for VIP and that this peptide may play a role in modulation of lymphocyte function. (Author abstract) (41 Refs)

30. REMOVAL OF THE SURFACE-BOUND HUMAN CHORIOGONADOTROPIN RESULTS IN THE CESSATION OF HORMONAL RESPONSES IN CULTURED LEYDIG TUMOR CELLS.

Segaloff DL, Ascoli M
Div. Endocrinology, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
J Biol Chem; 256(22):11420-11423 1981

The relationship between the binding and internalization of human choriogonadotropin and the stimulation of cAMP and steroid production was studied in cultured Leydig tumor cells. It was found that removal of the surface-bound hormone results in a rapid cessation of both cAMP and steroid production. We propose that the surface-bound hormone is responsible for the activation of steroidogenesis and that hormone internalization is involved in the deactivation of this process. (Author abstract) (17 Refs)

31. RADIOPROTECTIVE ACTIVITY AND SOME ASPECTS OF MECHANISM OF ACTION OF BIOGENIC AMINES IN MAMMALIAN CELLS CULTURED IN VITRO.

Graevskii EI, Ianushevskaia MI, Bueverova EI, Bragina EV, Konstantinova MM
N. K. Kol'tsov Inst. Biology of Development, Moscow, USSR
Radiobiologiia; 21(5):683-687 1981

The mechanism of radioprotective activity of the biogenic amines serotonin and adrenaline was studied in cultured Chinese hamster fibroblasts. Incubation of the fibroblasts with biogenic monoamines at 5 x 10(-3) M prior to irradiation with 300 R increased survival of the cells by approx 30%. A similar increase in survival was observed when the cells were incubated with serotonin after they were irradiated. Addition of serotonin prior to or after irradiation decreased the frequency of radiation-induced chromosome aberrations. Addition of adrenaline after irradiation failed to increase survival or to decrease the frequency of chromosome aberrations. (20 Refs) (In RUS)

32. LONG-TERM CULTURES IN POLYCYTHEMIA VERA AS PROOF OF DEPENDENCE ON ERYTHROPOIETIN.

Heilmann E, Holzknecht A, Fahrenkrug H, Essers U
Medizinische Poliklinik, Universitat Munster, Domagkstrasse 3, D-4400 Munster, W. Germany
Blut; 43(1):51-56 1981

Erythropoietin (EP)-dependence of erythroid colony proliferation was studied in eight patients with polycythemia vera (PV). Growth of colonies on methylcellulose ended after 3 wk in the absence of EP. With the addition of EP culture growth rose sharply in the first 2 wk, dropped in the 3rd wk, and then maintained a constant rate up to 9 wk. Apparently erythropoiesis in PV is EP-dependent. (18 Refs) (In GER)

EFFECTS OF ENDOGENOUS AND EXOGENOUS AGENTS ON NON-STEROID HORMONE ACTIVITY

33. THYROTROPIN-RELEASING HORMONE EXERTS RAPID NUCLEAR EFFECTS TO INCREASE PRODUCTION OF THE PRIMARY PROLACTIN MRNA TRANSCRIPT.

Potter E, Nicolaisen AK, Ong ES, Evans RM, Rosenfeld MG
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Proc Natl Acad Sci USA; 78(11,part2):6662-6666 1981

This report directly documents that a polypeptide hormone can regulate specific gene expression as a consequence of increasing the levels of a primary genomic transcript. The regulation and expression of the prolactin gene was studied in a cell line (GH4) derived from a rat pituitary tumor. These cells respond to addition of the hypothalamic tripeptide, thyrotropin-releasing hormone (TRH; thyroliberin), by elevation of the levels of mature prolactin mRNA and increase in prolactin biosynthesis. The message induction is preceded by, and apparently consequential to, a comparable rapid increase in the nuclear prolactin RNA precursors, including the putative primary transcript. (Author abstract) (38 Refs)

34. ADRENERGIC AND DOPAMINERGIC MODULATION GROWTH HORMONE AND PROLACTIN SECRETION IN NORMAL AND TUMOR-BEARING HUMAN PITUITARIES IN MONOLAYER CULTURE.

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J Clin Endocrinol Metab; 53(6):1278-1284 1981

Adrenergic and dopaminergic agonists administered in vivo stimulate GH secretion and inhibit PRL release. To investigate the direct effect of these agents on GH and PRL secretion from normal and tumor-bearing human pituitaries, they were added to monolayer cultures of surgically obtained pituitary tissue from patients with metastatic breast carcinoma, prolactinoma, and acromegaly. This study demonstrates that adrenergic and dopaminergic agonists directly inhibit normal human pituitary PRL and GH secretion. These findings are in contrast to the known in vivo GH stimulatory effect of these agents in man, which suggests that dopaminergically induced GH release may be mediated via the hypothalamus or higher central nervous system centers. In addition, dopaminergic defects exist in the adenomatous somatotrophs and lactotrophs of some patients with pituitary tumors. (36 Refs)

35. STIMULATION OF GROWTH HORMONE RELEASE BY VASOACTIVE INTESTINAL POLYPEPTIDE FROM HUMAN PITUITARY ADENOMAS IN VITRO.

Matsushita N, Kato Y, Katakami H, Shimatsu A, Yanaihara N, Imura H

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J Clin Endocrinol Metab; 53(6):1297-1300 1981

The effects of vasoactive intestinal polypeptide (VIP), TRH, dopamine, and rat median eminence extract on GH release from GH-secreting pituitary adenomas were studied in vitro using a sensitive superfusion method. Dispersed pituitary tumor cells obtained from three patients with acromegaly were placed in a superfusion column, and the amounts of GH in the superfusate were determined. The addition of VIP (10(-6) M) to the perfusion system resulted in a marked increase in GH release in all three cases, and a dose-response relationship in VIP (10(-8) -10(-6) M)-induced GH secretion was observed in one case studied. TRH (10(-7) M) and median eminence extract (1 equivalent/ml) also caused an abrupt and marked increase in GH release in all of the experiments. The infusion of either dopamine (10(-7) M) or bromocriptine (10(-7) M) inhibited GH secretion. These results suggest that VIP as well as TRH stimulate GH secretion by a direct action on GH-secreting pituitary tumor cells in at least some acromegalic patients. (Author abstract) (23 Refs)

36. BROMOCRIPTINE SUPPRESSES ACTH SECRETION FROM HUMAN PITUITARY TUMOUR CELLS IN CULTURE BY A DOPAMINERGIC MECHANISM.

Adams EF, Ashby MJ, Brown SM, White MC, Mashiter K
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Clin Endocrinol (Oxf); 15(5):479-484 1981

The effect of bromocriptine (BCR) on ACTH secretion from cell cultures of a human corticotropic adenoma and an ectopic ACTH secreting carcinoid tumor of the lung was examined. BCR (0.13-13.0 uM) significantly inhibited ACTH secretion in a dose-dependent manner when added to cultures of the corticotropic adenoma for 24 hr. The adenoma originated in a woman with Nelson's syndrome. BCR did not affect ACTH secretion from cells of lung carcinoid under identical conditions. BCR (1.3 uM) suppressed ACTH secretion from pituitary adenoma cells in a second experiment; the suppression was blocked by co-incubation of cells with haloperidol (HAL). HAL alone had no effect. Varying doses (0.013-13.0 uM) of serotonin or metergoline did not affect pituitary adenoma cell ACTH secretion during a 4 hr period, and 13.0 uM serotonin did not change BCR suppression during a 24 hr incubation. Dopamine (10.0 uM) significantly inhibited ACTH secretion from the pituitary adenoma cells during a 4 hr incubation, whereas lower doses had no effect. Results demonstrate a direct suppressive action of BCR on a human pituitary corticotropic adenoma through dopaminergic rather than serotoninergic mechanisms. (12 Refs)

37. EFFECT OF GROWING TUMOURS ON PINEAL MELATONIN LEVELS IN MALE RATS.

Lapin V, Frowein A
Inst. for Cancer Res., Univ. Vienna, Borschkegasse 8a, A-1090 Wien, Austria
J Neural Transm; 52(1/2):123-126 1981

The correlation between tumor growth and pineal body function was studied in male Wistar rats with transplanted Yoshida sarcoma. A 3-wk treatment with drugs interfering with biosynthesis of melatonin (Group A) and serotonin (Group B) started 24 hr after tumor transplantation. The drugs of Group A (melatonin, N-acetylserotonin, S-adenosylhomocysteine, and chlorpromazine) were injected daily at 5-6 pm, while the drugs of Group B (serotonin, 5-hydroxytryptophan, p-chlorophenylalanine, and nialamide) were injected daily at 8-9 am. The function of the pineal body was estimated by the pineal melatonin content. Negative correlation between tumor size and pineal melatonin content was observed in untreated rats as well as in rats treated with drugs of Groups A and B. Pinealectomy resulted in significant enhancement of tumor growth. (28 Refs)

38. RELEASE OF ERYTHROPOIETIN FROM MACROPHAGES BY TREATMENT WITH SILICA.

Rich IN, Anselstetter V, Heit W, Zanjani E, Kubanel B
Dept. Transfusion Medicine, Univ. Ulm, Ulm, W. Germany
J Supramol Struct Cell Biochem; 15(2):169-176 1981

Stimulation of murine macrophage-containing cell suspensions to produce an erythropoietic stimulating factor (ESF) by silicon dioxide (silica) was studied. Cell suspensions were prepared from the spleens of C57Bl mice. Samples consisting of 8 x 10(6) cells were incubated with 10(-4) gm silica/ml. ESF activity was measured in Swiss Webster mice using the polycythemic mouse (PCM) bioassay. Injection of 0.4, 0.8, or 1.6 ml of supernatant from silica-treated cell suspensions ip into PCM produced RBC 59Fe incorporation of 2.06%, 4.14%, and

10.43%, respectively. The activity of ESF was almost completely abolished by antiserum against erythropoietin (Ep). Erythropoietic response to Ep and purified samples of ESF were parallel. The presence of 1% fetal calf serum (FCS) in cell suspensions enhanced the effect of ESF compared to that produced in the absence of FCS. Incubation of cells with 2 mM Ca++ produced the same enhancement of ESF effect as FCS treatment. Results indicate that ESF is Ep and suggest for macrophages an important role in erythropoiesis. (19 Refs)

RECEPTOR/ BINDING SITES

39. THE 7315A PITUITARY TUMOR IS REFRACTORY TO DOPAMINERGIC INHIBITION OF PROLACTIN RELEASE BUT CONTAINS DOPAMINE RECEPTORS.

Cronin MJ, Valdenegro CA, Perkins SN, MacLeod RM
Dept. Physiology, Univ. Virginia Sch. Medicine, Charlottesville, VA, 22908
Endocrinology; 109(6):2160-2166 1981

The PRL-secreting pituitary tumor 7315a was grown in female rats, tested for its biological responsiveness and monitored for the presence of dopamine (DA) receptors under in vitro conditions. The basal PRL secretion from enzymatically dispersed tumor cells or fragments not treated with enzyme was 10-30 times less than that from dispersed or fragmented anterior pituitary cells which were continuously perfused in a cell column apparatus. Neither DA, its agonists pergolide and lisuride, nor the DA antagonist metoclopramide in the presence of agonist affected PRL release from the tumor cells. In contrast to these results, some dopaminergic agonists caused a dramatic inhibition of PRL release from the normal anterior pituitary cells, while coincubation with antagonists reversed the agonist effect. Thus, the tumor was refractory to DA agonist inhibition of PRL release. In contrast, TRH was capable of stimulating PRL secretion from both the tumor and the anterior pituitary cells. The binding of the DA antagonist [3H]spiperone to homogenates of the 7315a tumor was saturable, reversible, and stereoselective. The order of potency of a large variety of agonists and antagonists was characteristic of an interaction at a DA receptor and was highly correlated with the potencies previously reported for the DA receptor of the anterior pituitary. The guanine nucleotide 5'-guanylimidediphosphate reduced the affinity of the agonists DA, apomorphine, and 6,7-ADTN by 3-6 times, but had no effect on the affinity of the antagonists haloperidol, d-butaclamol, and l-sulpiride and the agonist bromocriptine. Although the 7315a pituitary tumor is refractory to DA agonist inhibition of PRL release, it possesses DA receptors; thus, a defect may exist at a postreceptor site in this tumor cell, in contrast to the GH3 cell line where there is no detectable receptor. (Author abstract) (25 Refs)

40. PHOTOAFFINITY LABELING OF THE INSULIN RECEPTOR IN H4 HEPATOMA CELLS: LACK OF CELLULAR RECEPTOR PROCESSING.

Hofmann C, Ji Tae H, Miller B, Steiner DF
Dept. Biochemistry, Univ. Chicago, Chicago, IL, 60637
J Supramol Struct Cell Biochem; 15(1):1-13 1981

The use of photoaffinity labeling to identify insulin-binding receptors in insulin-responsive, cultured monolayers of hepatoma cells and to determine their intracellular metabolic fate after binding was described. The process involved coupling of a photosensitive agent to highly purified insulin, iodination, binding to cellular receptors, and photoactivation. No degradation of insulin-receptor complexes was detected. (34 Refs)

41. LH(HCG) RECEPTOR IN BENIGN AND MALIGNANT TUMORS OF HUMAN OVARY.

Rajaniemi H, Kauppila A, Ronnberg L, Selander K, Pystynen P
Dept. Anatomy, Univ. Oulu, SF - 90220 Oulu 22, Finland
Acta Obstet Gynecol Scand [Suppl]; (101):83-86 1981

LH(hCG) receptors were identified with [125I]hCG in 38 benign and 26 malignant ovarian tumors of the human ovary. Eighteen percent of all the benign and 27% of all the malignant tumors were LH(hCG) receptor-positive. Four of 12 benign serous tumors and 3 of 17 benign mucinous tumors displayed definitive binding of [125I]hCG. Two Brenner tumors failed to bind [125I]hCG. Six of 21 malignant epithelial tumors displayed definitive binding of [125I]hCG. Only one out of four malignant granulosa cell tumors bound [125I]hCG, while the other six cord stromal tumors as well as one dysgerminoma failed to to bind [125I]hCG. LH(hCG) receptor content in the benign and malignant receptor-positive tumors was low compared with the normal ovarian tissue. The presence of LH(hCG) receptors in certain benign and malignant ovarian tumors may be a sign of the gonadotropic control of these tumors. The possible applications of these findings for the diagnosis and treatment of human ovarian tumors is discussed. (Author abstract) (15 Refs)

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CHARACTERIZATION OF NON-STEROID

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

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HORMONES IN EXPERIMENTAL AND IN VITRO SYSTEMS

1. HETEROGENEOUS FORMS OF THYROID-STIMULATING HORMONE IN MOUSE THYROTROPIC TUMOR AND SERUM: DIFFERENCES IN RECEPTOR-BINDING AND ADENYLATE CYCLASE-STIMULATING ACTIVITY.

Pekonen F, Carayon P, Amr S, Weintraub BD
(c/o Weintraub), NIH, Building 10, Room 8N315, Bethesda, MD, 20205
Horm Metab Res; 13(11):617-620 1981

Thyroid-stimulating hormone (TSH) in tumor and serum of mice with thyrotropic tumors was studied by radioimmunoassay (RIA), radioreceptor assay (RRA) and thyroid adenylate cyclase assay (ACA). In unfractionated samples, serum TSH displayed significantly higher ACA/RIA (0.69 + -0.10) and ACA/RRA ratios (0.79 + -0.04) than TSH in tumor extracts (0.45 + -0.05 and 0.31 + -0.01, respectively). After gel chromatography, both tumor and serum TSH activity measured in RIA and RRA eluted in broad, heterogenous peaks with an apparent mol wt range of 26,000-44,000 daltons. The ACA activity of tumor TSH eluted in two sharp peaks (26,000 and 44,000) while that of serum TSH eluted in three peaks (26,000, 33,000 and 44,000). The ACA/RIA and ACA/RRA ratios varied greatly among the chromatography fractions, the lowest ratios being detected in the tumor TSH of 33,000 daltons (0.02 for each) and the highest ratios in both tumor and serum TSH of 26,000 (ACA/RIA = 1.60-1.90, ACA/RRA = 1.12-1.20). Since previous biosynthetic studies have suggested that such heterogeneous forms of mouse tumor TSH differ solely in carbohydrate content, our data suggest that the biologic activity of TSH may be modulated by its glycosylation. (Author abstract) (21 Refs)

2. MULTIPLE FORMS OF IMMUNOREACTIVE BETA-ENDORPHIN ARE PRESENT IN AN ECTOPIC ADRENOCORTICOTROPIN-PRODUCING TUMOR BUT NOT IN NORMAL PITUITARY OR PITUITARY ADENOMAS.

Suda T, Tozawa F, Yamaguchi H, Shibasaki T, Demura H, Shizume K
Dept. Medicine, Tokyo Women's Medical Coll., 10-Kawada-Cho, Ichigaya, Shinjuku-ku, Tokyo 162, Japan
J Clin Endocrinol Metab; 54(1):167-171 1981

Human ACTH-producing tumor and plasma have been examined by gel filtration and ion exchange chromatography to detect the possible presence of reported multiple forms of immunoreactive beta-endorphin (I-EP). Ion exchange chromatography of I-EP obtained from gel filtration showed four components of I-EP [2 major peaks in the positions of EP-(1-31) and EP-(1-27) and 2 minor peaks in the positions of N-acetyl EP-(1-31) and N-acetyl EP-(1-27)] in two ectopic ACTH-producing lung cancers, and two components of I-EP [the major peak in the position of EP-(1-31) and the minor peak in the position of N-acetyl EP-(1-31)] in an ectopic ACTH-producing thyroid cancer. Only a single peak in the position of EP-(1-31) was present in plasma from a patient with Nelson's syndrome and a patient with Addison's disease, in the pituitary adenomas from six patients with Cushing's disease, and in the nontumorous pituitary tissues from a patient with Cushing's disease and a patients with acromegaly. These data suggest that the post-translational processing of EP in human pituitary is different from that in the ectopic ACTH-producing tumor. (Author abstract) (12 Refs)

3. HUMAN LYMPHOCYTE PRODUCTION OF CORTICOTROPIN AND ENDORPHIN-LIKE SUBSTANCES: ASSOCIATION WITH LEUKOCYTE INTERFERON.

Smith EM, Blalock JE
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Proc Natl Acad Sci USA; 78(12):7530-7534 1981

Human leukocyte interferon (hIFN-alpha) preparations contain immunologically and biologically recognizable endorphin and corticotropin-like (ACTH-like) activities. The ACTH bioactivity was demonstrable only after pepsin or acid treatment. Highly purified hIFN-alpha was composed of two molecular species of interferon (18,500 and 23,000 daltons). Endorphin activity was associated with both of these molecules. Pepsin treatment of the 23,000-dalton but not the 18,500-dalton hIFN-alpha generated ACTH activity. In acid, the 23,000-dalton hIFN-alpha broke down into the 18,500-dalton form and ACTH (4,500 daltons). The ACTH derived from hIFN-alpha by pepsin digestion comigrated with a purified ACTH standard in NaDodSO4/polyacrylamide gel electrophoresis. hIFN-alpha-producing lymphocytes showed positive immunofluorescence after staining with highly specific antisera to ACTH-alpha-(1-13) and gamma-endorphin. Essentially 100% of the human peripheral lymphocytes were capable of producing both ACTH and gamma-endorphin-related substances, presumably associated with hIFN-alpha. These results strongly suggest a circuit between the immune and neuroendocrine systems which involves neuroendocrine hormone-like substances, some of which are associated with hIFN-alpha. (Author abstract) (27 Refs)

4. NEUROPHYSIN BIOSYNTHESIS IN VITRO IN OAT CELL CARCINOMA OF THE LUNG WITH ECTOPIC VASOPRESSIN PRODUCTION.

Yamaji T, Ishibashi M, Katayama S, Itabashi A, Ohsawa N, Kondo Y, Mizumoto Y, Kosaka K
Third Dept. Internal Medicine, Univ. Tokyo, Hongo, Tokyo 113, Japan
J Clin Invest; 68(6):1441-1449 1981

The incorporation of labeled compounds into neurophysins of a transplantable human oat cell carcinoma of the lung with ectopic vasopressin production was studied in vitro. Neurophysins in cell extracts and in incubation media were isolated by immunoprecipitation and analyzed by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis. When cells were incubated with L-[35S]cysteine for 12 hr, SDS-polyacrylamide gel electrophoresis of the immunoprecipitates from cell extract and medium resolved two forms of neurophysins with apparent mol mass of 10,000 (10K) and 20,000 (20K). Both forms of [35S]neurophysins were completely displaced from the immunoprecipitates by excess human neurophysin. Incubation of cells with L-[35S]cysteine and D-[3H]glucosamine hydrochloride revealed that glucosamine was incorporated into the 20K neurophysin region, but not into 10K species. To observe the kinetics of labeling of the two forms of neurophysins, cells were incubated with L[35S]cysteine for varying periods of time. After short labeling periods, most of the radioactivity resided in 20K species, which plateaued after 1 hr, whereas 10K neurophysin progressively increased in its height. When cells were chased with unlabeled cysteine after the exposure to a short pulse of labeling, 20K neurophysin peak gradually decrea sed with an apparent initial half-life of 1 hr. In contrast, the label in 10K neurophysin steadily increased, which exceeded the former by 3 hr of chase. Analysis of 20K neurophysin in cell extract by isoelectric focusing on polyacrylamide gel demonstrated that it was principally composed of a protein with an apparent isoelectric point (pI) of 5.7. These results suggest that neurophysin is synthesized in ectopic vasopressin-producing tumors by post-translational processing from a glycosylated proneurophysin with an apparent molecular mass of 20,000 daltons and a pI of 5.7. (Author abstract) (28 Refs)

5. A MULTIHORMONAL TUMOR OF THE PANCREAS PRODUCING NEUROTENSIN.

Feurle GE, Helmstaedter V, Tischbirek K, Carraway R, Forssmann WG, Grube D, Roher HD

Medizinische Poliklinik, Univ. Heidelberg, Hospitalstrasse 3, 6900 Heidelberg, W. Germany

Dig Dis Sci; 26(12):1125-1133 1981

In a pancreatic adenoma approximately 78.7% of the endocrine cells reacted specifically with antisera to neurotensin, 17.5% to gastrin, 2.8% to pancreatic polypeptide, and 1% to glucagon. The electron microscope revealed that the majority of the endocrine cells were N-cells -- morphologically similar to the ileal N-cells which are known to represent the neurotensin-producing cells. Neurotensin was extracted from the tumor and identified by Sephadex, ion-exchange, and high-pressure liquid chromatography. Gastrin, pancreatic polypeptide, and glucagon cells were also identified by the electron microscope; the peptides were extracted and demonstrated by chromatography. The serum concentrations of these hormones were elevated. After total gastrectomy which was necessary because of Zollinger-Ellison syndrome, a jejunoesophageal alkaline reflux, reaching the upper esophagus appeared. As intravenous infusion of synthetic neurotensin in rats caused an increase of luminal enteric pressure, it is suggested that severe jejunoesophageal reflux after gastrectomy may be a clinical feature of a neurotensinoma. (Author abstract) (24 Refs)

6. NEUROENDOCRINE DIFFERENTIATION IN BASAL CELL CARCINOMAS.

Dardi LE, Memoli VA, Gould VE

(c/o Gould) Dept. Pathology, Rush-Presbyterian-St. Luke's Medical Center, 1753 West Congress Parkway, Chicago, IL, 60601

J Cutan Pathol; 8(5):335-341 1981

Ten consecutive cases of basal cell carcinomas were reviewed. Nine of these displayed the typical histology of basal cell carcinoma, the other case was composed of small spindle to ovoid cells with scant cytoplasm and a high mitotic rate, resembling an 'oat cell' carcinoma. These were studied using the immunoperoxidase technique for tissue localization of calcitonin, insulin, glucagon, somatostatin, ACTH, gastrin and nerve growth factor. Three cases were negative for all hormones tested. Three cases were focally positive for a single hormone; one each for calcitonin, somatostatin, and ACTH. Two cases were focally positive for ACTH and somatostatin and two cases were focally positive for calcitonin, somatostatin and ACTH. None of the other hormones displayed activity. The positive staining was eliminated after absorption by the specific antigen. This immunohistochemical study illustrated neuroendocrine differentiation in basal cell carcinomas as has previously been suggested by the Grimelius stain and electron microscopy. Thus, as demonstrated in other epithelial neoplasms, basal cell carcinoma may also display neuroendocrine differentiation. This illustrates the potential multidirectional differentiation in neoplastic epithelial cells. (Author abstract) (23 Refs)

7. IMMUNOCHEMICAL STUDIES ON THYMOSIN: RADIOIMMUNOASSAY OF THYMOSIN ALPHA1.

McClure JE, Lameris N, Wara DW, Goldstein AL

Dept. Biochemistry, George Washington Univ. Sch. Medicine and Health Sciences, Washington, DC, 20037

J Immunol; 128(1):368-375 1982

A sensitive and specific radioimmunoassay (RIA) has been developed to measure thymosin alpha1 in human blood and tissue extracts. Thymosin alpha1, originally isolated from bovine thymosin fraction 5, has an identical primary structure in bovine and human species. Antiserum to synthetic thymosin alpha1 was prepared in rabbits. A synthetic analogue, N-Ac-(Tyr(1))thymosin alpha1 was radioiodinated by utilizing Na125I and soluble lactoperoxidase. The RIA is capable of detecting as small an amount as 40 pg thymosin alpha1 in serum/plasma and does not significantly cross-react with other putative thymic hormones or other purified blood proteins that have been assayed. Proteolytic degradation of thymosin alpha1 does not occur during the collection, storage, or assay of serum or plasma. The concentration of thymosin alpha1 in the blood is highest in utero, decreases sharply after birth, and appears to remain fairly constant during the first 15 yr of life. Maternal blood levels of thymosin alpha1 appear to be above normal during pregnancy. (Author abstract) (28 Refs)

8. NEUROHORMONAL PEPTIDES IN OVARIAN CARCINOIDS: AN IMMUNOHISTOCHEMICAL STUDY OF 81 PRIMARY CARCINOIDS AND OF INTRAOVARIAN METASTASES FROM SIX MID-GUT CARCINOIDS.

Sporrong B, Falkmer S, Robboy SJ, Alumets J, Hakanson R, Ljungberg O, Sundler F

Dept. Obstetrics and Gynecology, Malmo General Hosp., S-214 01 Malmo, Sweden

Cancer; 49(1):68-74 1982

Eighty-one primary ovarian carcinoids and intraovarian metastases from six mid-gut carcinoids were examined for the presence of tumor cells immunoreactive with antisera raised against various neurohormonal peptides, mostly of gastroenteropancreatic (GEP) origin. Twenty of the primary and two of the metastastic carcinoids contained such tumor cells. The incidence of tumors with any kind of neurohormonal peptide immunoreactive tumor cells was 53% in the trabecular carcinoids, and 42% in the strumal carcinoids, whereas the incidence was much lower (7%) in the insular type. Immunoreactive pancreatic polypeptide (PP), glucagon, enkephalin, and somatostatin were those neurohormonal peptides most commonly observed in the tumor cells of the primary carcinoids. Those less commonly found were substance P, calcitonin, VIP, neurotensin, beta-endorphin, and ACTH. Four metastatic carcinoids were nonreactive with all the antisera used. Cells storing immunoreactive insulin, glucagon, PP, VIP, gastrin, substance P, or enkephalin were found in one of the two remaining metastatic carcinoids; in the other only gastrin-immunoreactive tumor cells were observed. The occurrence and distribution of tumor cells storing the neurohormonal peptides in ovarian carcinoids are discussed in relation to their possible origin in the ovary and to carcinoids in the gut. (Author abstract) (32 Refs)

9. HUMAN CHORIONIC GONADOTROPIN SUBUNIT MEASUREMENT IN PRIMARY HYPERPARATHYROIDISM.

Stock JL, Weintraub BD, Rosen SW, Aurbach GD, Spiegel AM, Marx SJ
NIH, Building 10, Room 9D20, Bethesda, MD, 20205
J Clin Endocrinol Metab; 54(1):57-63 1982

The concentration of subunits of hCG (hCG alpha and hCG beta) was determined in plasma or serum from 70 patients with primary hyperparathyroidism (1 degree HPT). Two of three patients with parathyroid carcinoma showed elevation in plasma concentrations of both subunits, which fell after surgical removal of the tumor. An extract prepared from the tumor of one of these patients contained the subunits in high concentrations, whereas in extracts similarly prepared from tissues removed from seven patients with benign 1 degree HPT, the subunits were not detectable or were present in much lower concentrations. In 42 cases of benign 1 degree HPT, samples from veins containing a 10-fold gradient of parathyroid hormone obtained during selective venous catheterization and peripheral samples from the same patients were analyzed for hCG subunits. Only one patient demonstrated a mild elevation of hCG alpha in parathyroid venous effluent alone that may have represented subunit release by apparently benign parathyroid tissue. Thirty patients with multiple endocrine neoplasia type I were tested; eight evidenced clinically active islet cell tumors, and six of these eight showed high circulating concentrations of hCG alpha (and hCG beta in one case). Patients in the multiple endocrine neoplasia type I group with 1 degree HPT or pituitary tumors, but no evident pancreatic islet disease, did not show elevations in subunit concentrations. Thus, in patients with 1 degree HPT, determination of subunits of hCG may be helpful in making the diagnosis of parathyroid carcinoma or in screening for associated (and probably malignant) pancreatic islet disease. (Author abstract) (36 Refs)

10. HUMAN CHORIONIC GONADOTROPIN RADIOANTIBODIES IN THE RADIOIMMUNODETECTION OF CANC ER AND FOR DISCLOSURE OF OCCULT METASTASES.

Goldenberg DM, Kim EE, DeLand FH
Div. Experimental Pathology, Dept. Pathology, Univ. Kentucky and Veterans Admin. Medical Centers, Lexington, KY, 40536
Proc Natl Acad Sci USA; 78(12):7754-7758 1981

Radioimmunodetection (RaID) of tumors containing human chorionic gonadotropin (hCG; choriogonadotropin) was evaluated in 25 patients by injecting 131I-labeled goat antibody IgG against hCG and performing total-body photoscans with a gamma-scintillation camera 24 and 48 hr later. All 10 testicular cancer patients with proven tumor sites had positive RaID results, whereas three cases without known tumor were negative. Four patients with hydatidiform mole and one with degenerative products of conception showed positive RaID results consistent with elevated serum hCG titers. Two putatively false-positive results were obtained in patients with lung or ovarian cancer, whereas a false-negative metastasis to the liver of a patient with lung cancer and an elevated serum hCG titer was observed. Of 14 tumor sites found by RaID in 10 testicular cancer patients, 4 were revealed by RaID prior to any other detection method used and provided a lead time to definitive diagnosis by other measures of a few days to greater than 1 yr. Although a number of patients had high serum hCG levels, even exceeding 3 ug/ml, the xenogeneic antibody was capable of localizing in tumor. No adverse effects were noted in any of the patients studied. Thus, hCG RaID appears to be a safe and effective method of detecting and locating hCG-producing tumors and has been found to disclose occult testicular cancers. (Author abstract) (26 Refs)

11. RADIOIMMUNOASSAY OF HUMAN CHORIONIC GONADOTROPIN.

Majali MA, Shah KB, Mani RS
Radiopharmaceuticals section, Bhabha Atomic Res. Centre, Trombay, Bombay, India
J Radioanal Chem; 65(1/2):287-295 1981

A radioimmunoassay technique for determination of serum levels of human chorionic gonadotropin (HCG) is described. HCG is labeled with 125I (80-120 uCi/mg). Bound and free hormone are separated using 74% aqueous dioxane. Sensitivity of the method is approx 1.5 milliIU/ml HCG. Variation is less than 5% intra-assay and less than 12% inter-assay. (13 Refs)

CLINICAL, DIAGNOSTIC AND PROGNOSTIC STUDIES

12. PLASMA PROLACTIN LEVELS IN PATIENTS WITH BREAST CANCER.

Rose DP, Pruitt BT
Div. Clinical Oncology, Wisconsin Clinical Cancer Center, 600 Highland Ave., Madison, Wisconsin, 53792
Cancer; 48(12):2687-2691 1981

The plasma prolactin levels of 98 healthy women 22 to 65 years old showed a strong inverse correlation with age. This relationship persisted for older premenopausal and postmenopausal women (aged 30 to 65 years) whose results were compared with those of 34 premastectomy early breast cancer patient s, another 38 studied 4 to 6 weeks after mastectomy, and 38 with advanced disease (age range, 30 to 77 years). There was no correlation between age and plasma prolactin in any of the breast cancer groups. When patients and controls were classified according to their menopausal status, the premastectomy and postmastectomy early breast cancer groups both showed significantly higher prolactin concentrations than the corresponding controls (p less than 0.001 in all cases). These abnormalities were particularly prominent in the patients studied after surgery, although the difference was significant only for the postmenopausal groups (p less than 0.05). Plasma cortisol and urinary free cortisol levels were normal in postmastectomy patients, suggesting that stress was not the cause of elevated prolactin levels. In advanced breast cancer, elevated plasma prolactin concentrations were found only in the postmenopausal patients. (Author abstract) (32 Refs)

13. THERAPEUTIC CONSIDERATIONS AND PROGNOSIS OF PROLACTINOMAS.

Mancini AM
Universidad de Buenos Aires, Buenos Aires, Argentina
Prensa Med Argent; 68(10):404-406 1981

Prolactin (PL) radioimmunoassay permits better understanding of physiopathological mechanisms and evolution of prolactinomas. Clinical, ophthalmological, biochemical, and radiological factors should be evaluated in the diagnosis of these tumors. Therapeutic considerations should include the following: the involvement of the hypothalamus and hypophysis; simple radiography; hypocycloid tomography; computed tomography; pneumocisternography; arteriography; biochemical aspects of circadian rhythm, stimulation with metoclopramide and thyrotropin-releasing hormone, and inhibition with bromoergocryptine (BEC) and sulpiride and ophthalmological symptoms. Therapeutic choices for microadenomas include transsphenoidal (TS) microsurgery (followed by irradiation in some cases of elevated PL) and administration of BEC. If, 6 mo after the surgery, the PL levels do not return to normal, administration of the BEC should be started. When pregnancy occurs in the patients, they should have regular controls and lactation should be avoided, since lactation is the greatest stimulant of production of prolactin. In patients with larger tumors subfrontal (SF), the combination of SF and TS routes should be used for the resection of the tumor. The prognosis decreases with increasing size of tumor and PL level. Early diagnosis improves the prognosis. (12 Refs) (In SPA)

14. ENDOCRINOLOGIC ASPECTS OF BREAST CANCER RISK AND FIBROCYSTIC MASTOPATHY (MEETING ABSTRACT).

Tarquini B, Cecchettin M, Rosselli del Turco M, Cariddi A, Cavallini V, Nunnari G, Ciatto S
Ist Clin Med II, Cattedra di Semeiotica Medica, Univ Firenze, Florence, Italy
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy Italian Society of Endocrinology; :A40 1981

Fibrocystic disease of the human breast (FM) is obviously not a sufficient condition for the development of breast cancer (BC) because it is so common in comparison with the incidence of BC. Nevertheless FM is claimed to be a major risk factor involved in BC. A number of studies suggest that potential malignancy is related not only to histologic features but the other factors also intervene: 1) 14 women with histologically validated FM; 2) 14 women apparently healthy and without known risk factors (control groups); 3) 4 women with known FM and very high risk for BC. On each serum sample, Prolactin, thyroid stimulating hormone (TSH), luteinizing hormone (LH) follicle stimulating hormone (FSH), Gastrin, 17-beta-estradiol, Calcitonin and parathyroid hormone (PTH) were evaluated by radioimmunoassay kits. Each subject was sampled during the intermenstruum. Seven patients with FM and 7 controls were sampled 4 x in a yr with selection of the season of sampling. Some FM patients showed differences in serum levels of Prolactin, TSH, LH and PTH suggesting changes in combined risk. These results and related ethical problems in very high risk women are discussed. (no Refs)

15. HORMONAL PATTERN AND SEX HORMONE BINDING GLOBULIN IN PLASMA OF WOMEN WITH CYSTIC BREAST DISEASE (MEETING ABSTRACT).

Berta L, Frairia R, Bumma C, Navello C, Mossetti C, Rovero E, Gaidano G
Patologia Speciale Medica B and Clinica Medica B, Univesita di Torino, Torino, Italy
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy Italian Society of Endocrinology; :A25 1981

Fibrocystic mastopathy is a benign disease of fertile women, considered as a clinical condition at high risk for breast cancer. Etiopathogenesis is still uncertain but often the clinical onset has been related to plasma sex hormone imbalance. Sex Hormone Binding Globulin (SHBG) could be also involved. Recently SHBG has been hypothized to play a significant role in breast cancer development. The aim of present work was to study plasma hormonal pattern (E1; E2; P; prolactin, PRL) with respect to Sex Hormone Binding Globulin binding capacity (SHBG-bc) in fertile women with fibrocystic breast disease. In plasma of 57 women with fibrocystic breast disease (aged 18-42 yr) and of 30 normal control women (aged 21-45 yr) the following parameters have been evaluated: E1, E2, P, PRL by radioimmunoassay (RIA) (Biodata); SHBG-bc by an equilibrium partition technique (PEG/Dextran). All subjects were studied in the luteal phase of the menstrual cycle: they had body wt in normal range and were free from endocrinological, hepatic or renal diseases. Progesterone plasma levels significantly lower in patients than in controls are according to the data observed by Mauvais-Jarvis et al and confirm the hypothesis that altered ratio Estrogens/Progesterone interferes in the onset of the disease. Estradiol-17-beta and estrone plasma levels in our cases do not show significant difference, but SHBG-bc is lower in the patients than in normal subjects. These data support that Progesterone and SHBG-bc deficiency respectively induce a relative increase of estrogen plasma levels, influencing mammary epithelium proliferation. (no Refs)

16. HIGH (H) VERSUS LOW (L) DOSE MEDROXYPROGESTERONEACETATE (MPA) IN ADVANCED BREAST CANCER (MEETING ABSTRACT).

Cavalli F, Goldhirsch A, Kaplan E, Alberto P
Group for Clinical Cancer Research, 1205 Geneva-CH, Switzerland
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

H dose MPA was recently reported to yield an impressive response rate (RR) in the treatment (Rx) of advanced breast cancer. Therefore 165 postmenopausal patients (pts) with measurably advanced breast cancer (20% without prior treatment (Rx)) were randomized between 100 mg/daily (H) and 500 g twice weekly (L) MPA im for 4 wk: responding pts were continued on 500 mg MPA im once weekly. During Rx MPA blood levels were determined every 2-4 wk in 9 pts. (5 H, 4 L), in 21 pts (12 H, 9 L) serum follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E1) and, sex hormone binding hormone (SHBG) were measured monthly. MPA blood levels were consistently and at least twofold higher in pts treated with H, with steady-state levels reached after 4 wk. Preliminary results of the hormonal determinations show a significant decrease of FSH/LH and a marginal increase of PRL during Rx, without clear correlation with H or L dose. At the last cut-off (2/81) 127 pts were already evaluable. Clincal prognostic factors (age, free interval, number and site of metastasis (mets), type of previous Rx and response to it) were well balanced between H and L: Hormone receptors were known only in 1/3 of pts. Partial response (PR) was observed in 20/64 (30%) pts with H MPA and 7/62 (11%) in L MPA (RR: H vs L p less than 0.05). The more pronounced difference in RR was found in pts refractory to prior Rx (PR: 12/57 in H, 0/53 in L) or with osseous mets. (PR: 8/20 in H, 1/19 in L). Median duration of PR was 230+ d in H and 150+ d in L. A no change for a median duration of 128 d was observed in 28 pts: 14 in H, 14 in L. These data tend to support the therapeutic superiority of H over L MPA. A final evaluation of all clinical and endocrinologic results is currently underway. (no Refs)

17. EFFECTS OF ETHYNYLESTRADIOL ADMINISTRATION ON GONADOTROPIN LEVELS AND CLINICAL EVALUATIONS IN PATIENTS WITH PROSTATIC CANCER.

Maruta H, Kumamoto Y
Dept. Urology, Sapporo Medical Coll., Sapporo, Japan
Hinyokika Kiyo; 27(9):1133-1142 1981

Serum LH and FSH were measured by radioimmunoassay in five patients with prostatic cancer following castration and oral ethynylestradiol administration. Serum acid phosphatase levels of 10 patients were also examined to evaluate the clinical efficacy of ethynylestradiol for treating the prostatic cancer. Of four castrated patients who received the ethynylestradiol at the dose of 0.15 mg/day for 10-14 days, LH and FSH levels of two patients were suppressed significantly, but were not suppressed to the level of prepubertal value. LH and FSH of two other patients were not suppressed at the dose of 0.15 mg/day. To suppress the gonadotropin of castrated male completely to the prepubertal level, it was needed to administer the ethynylestradiol at the dose of 1.5 mg/day for about 20 days. Of nine patients who showed the elevated acid phosphatase level before treatment, one patient showed normal level after castration, the acid phosphatase levels of five other patients became normal following the castration and ethynylestradiol administration. From the finding of normal acid phosphatase level following ethynylestradiol administration, ethynylestradiol was considered to be the effective drug for the prostatic cancer. (Author abstract) (11 Refs) (In JPN)

18. PITUITARY FUNCTION AND GROWTH OF CHILDREN UNDER LEUKEMIA TREATMENT.

Schuler D, Gacs G, Revesz T, Koos R, Keleti J
II. Gyermekklinika, Semmelweis Orvostudomanyi Egyetem, Tuzolto u. 7-9, H-1094 Budapest, Hungary
Monatsschr Kinderheilkd; 128(12):773-775 1981

The effect of cranial irradiation (total dose 2,400 or 4,800 rads, individual dose 150 wk within 3 wk) on the pituitary function of 40 children (2-14 yr old) with acute lymphoblastic leukemia was studied 1-3 yr after radiotherapy. Corticosteroids were not administered. The plasma growth hormone level, determined after arginine stimulation in 15 children, was normal in 13. The basal thyroid stimulating hormone level was normal in all cases, but its rise following administration of thyrotropin-releasing hormone was subnormal in 13/15 cases. The patients with subnormal growth hormone levels and subnormal thyroid stimulating hormone levels were not identical. The increase in the urinary excretion of ketogenic steroids under the effect of metyrapone was normal in all cases. The growth, monitored in 40 children, was normal in all cases compared with that of healthy controls. (11 Refs) (In GER)

19. CIRCULATING ANTI-ADRENOCORTICOTROPIN-ADRENOCORTICOTROPIN IMMUNE COMPLEXES IN PATIENTS WITH SMALL-CELL CARCINOMA OF THE LUNG (MEETING ABSTRACT).

Luster W, Gropp C, Havemann K
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UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland . International Union Against Cancer 131 pp., 1981.

The ectopic production of peptide hormones, partly marking paraneoplastic syndromes, in patients with lung cancer, especially in small-cell carcinoma, has been reported. Circulating immune complexes were described to be associated with small-cell carcinoma. Both phenomena may play a role in pathogenetic proliferation of this tumor. The present study was designed to investigate whether there is a correlation between these two findings. In sera of more than 190 patients with lung cancer of various histologic types ACTH was determined by radioimmunoassay. In 35% of all cases with small-cell carcinoma elevated ACTH levels were exhibited. In sera of those patients IgG-ACTH-immune complexes were isolated by affinity chromatography on protein A-sepharose or by polyethylene glycol precipitation. Though calcitonin is the peptide hormone, which shows the highest frequency associated with the small-cell carcinoma, there was no calcitonin immunoreactivity provable in the immuncomplex fraction. In sera of some patients without any demonstrable ACTH, free antibodies against ACTH were detected by titration in two radioimmunoassays. In patients with elevated ACTH levels before therapy, after response to therapy, a decrease of measurable ACTH corresponding with an increase of free ACTH-antibodies was shown. These results suggest that there is a connection between the ectopic production of autoimmunoreactive ACTH by a tumor and the formation of circulating ACTH-IgG immune complexes. (no Refs)

20. ECTOPIC ACTH PRODUCTION WITH AUTOANTIBODY FORMATION IN A PATIENT WITH ACUTE MYELOBLASTIC LEUKEMIA.

Pfluger KH, Gramse M, Gropp C, Havemann K
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N Engl J Med; 305(27):1632-1636 1981

The case history of an acute myeloblastic leukemia (AML) patient with abnormal ACTH production and autoantibody formation is presented. Symptoms included anemia and slowly healing skin lesions. Differential blood profile revealed 60% lymphocytes, 30% blasts, and 10% granulocytes. Blood chemistry was abnormal; ACTH levels were 1960 picog/ml. Bone marrow was characteristic of AML. Therapy included doxorubicin, vincristine, and cytarabine. Remission followed, ACTH levels decreased but never reached normal levels. A subsequent marked rise in ACTH was unaccompanied by indications of relapse. A relapse did occur eventually; during relapse ACTH levels were about the same as during remission. Gradually the disease became progressive. No adenoma of pituitary or adrenal glands was revealed after death. The frequency of elevated ACTH in acute leukemia patients was also investigated by radioimmunoassay of serum, ultracentrifugation, polyacrylamide gel electrophoresis, and cell culture. Results showed only marginally elevated ACTH levels in most patients with various types of hemoblastosis. Apparently ectopic ACTH is produced in the leukemia cells. (31 Refs)

21. EXPERIENCE WITH SELECTIVE VENOUS SAMPLING IN DIAGNOSIS OF ACTH-DEPENDENT CUSHING'S SYNDROME.

Drury PL, Ratter S, Tomlin S, Williams J, Dacie JE, Rees LH, Besser GM
Dept. Endocrinology, St. Bartholomew's Hosp., London EC1A 7BE, England
Br Med J; 284(6308):9-12 1982

Twenty-three patients with ACTH-dependent Cushing's syndrome were subjected to selective venous catheterization and sampling for ACTH on a total of 26 occasions. Out of 10 patients with pituitary-dependent disease, 9 had raised ACTH concentrations in one or both high internal jugular vein samples. Eight patients had 11 proved sites of ectopic hormone production: of these, 6 were correctly identified by the sampling technique, and in 4 of them this was the only accurate method of localization. The results of one catheterization were misleading, and on 10 occasions they were inconclusive; five patients remained undiagnosed by any method. Overall, 15 of the 26 catheterizations provided diagnostically valuable information. Selective venous catheterization and sampling for ACTH is effective in confirming a pituitary source of the hormone and may be valuable in locating the source of ectopic ACTH production in some cases. (Author abstract) (21 Refs)

22. PERSISTENCE OF CUSHING'S SYNDROME AFTER HYPOPHYSECTOMY.

Federman DD, Mark EJ, Simeone JF, Ridgway EC, Scully RE, Daniels GH, Calderwood SB
Professor Medicine, Harvard Medical Sch., MA
N Engl J Med; 305(27):1637-1643 1981

Case history, discussion, and differential diagnosis of a patient (male, 23 yr old) with suspected Cushing's syndrome are presented. Symptoms were puffy appearance, decreased muscle strength, easy bruising, and a slight increase in wt. Physical examination revealed hypertension, tremor of the hands, pink striae over the buttocks, and pedal edema. Earlier tests had shown the fasting cortisol level to be 20 ug/100 ml and the fasting ACTH level 102 picog/ml. An x-ray of the chest had revealed a 1.5 cm nodule. Further tests revealed abnormal response in human growth hormone (less than 1-1.8 nanog/ml), thyroid stimulating hormone (2.5-3.8 microU/ml), prolactin (4.9-4.7 nanog/ml), and cortisol secretion (47-56 ug/100 ml). A transsphenoidal operation was performed and an apparent microadenoma was removed. The symptoms persisted and the patient was maintained on prednisone, levothyroxine, propranolol, and chlorthalidone. After discontinuation of prednisone and levothyroxine the patient developed mild muscular weakness, cold intolerance, coarse, dry skin, and arthralgia of the knees and fingers. Serum cortisol and plasma ACTH levels ranged from 8.0-10.0 ug/100 ml and 28-53 picog/ml, respectively; after dexamethasone therapy they decreased to 0.7 ug/100 ml and 7 picog/ml, respectively. Clinical diagnosis was Cushing's syndrome secondary to bronchial carcinoid. Follow up after tumor extraction revealed extremely high levels of ACTH. Cortisol levels remained low; prednisone therapy was instituted and tapered over 3-4 mo and then discontinued. The patient is now normal biochemically and has lost many of the cushingoid features. (25 Refs)

23. ELEVATION OF PLASMA ANTIDIURETIC HORMONE (ADH) ASSOCIATED WITH CHEMOTHERAPY-INDUCED EMESIS IN MAN.

Fisher RD, Rentschler RE, Nelson JC, Godfrey TE, Wilbur DW
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Cancer Treat Rep; 66(1):25-29 1982

Eleven randomly hydrated patients with metastatic malignancies received iv bolus chemotherapy. Serial observations of plasma antidiuretic hormone (ADH), serum osmolality, blood pressure, and presence of nausea or emesis were made over the next 3-4 hours. Group 1 (4 patients) had no nausea or emesis and no change in ADH, osmolality, or mean blood pressure. Group 2 (7 patients) had nausea and emesis following chemotherapy, with an increase in mean ADH from a baseline level of 5.53 pg/ml to a peak after emesis of 33.83 pg/ml. Group 2 had no significant increase in osmolality or decrease in mean blood pressure before emesis. ADH levels increased 0-40 minutes before emesis and peaked 28-115 minutes (mean, 66) after emesis. Emesis caused by chemotherapy agents is associated with rapid, significant increases in plasma ADH levels, independent of changes in osmolality or blood pressure. (Author abstract) (9 Refs)

24. THE MANAGEMENT OF RADIATION-INDUCED TUMOURS OF THE THYROID.

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Univ. Chicago Pritzker Sch. Medicine, Univ. Chicago Hosp. and Clinics, Chicago, IL
Clin Endocrinol Metab; 10(2):299-315 1981

Procedures are explained for the management of thyroid tumors found in patients who have undergone neck irradiation in childhood. Management begins with the physical examination; patients with normal thyroid and no symptoms are advised to submit to re-examination every 2 yr and receive no further treatment. Patients with equivocal results of physical examination or with diffusely enlarged thyroids are given 99Tc pinhole-camera scintigraphy; those whose thyroids show diffuse uptake have thyroid tests and appropriate treatment and those whose thyroids exhibit a distinct nodule enter the same management path as those whose thyroids revealed distinct nodules on earlier physical examination. Total extracapsular lobectomy is followed by frozen section biopsy to determine the existence of malignancy. Benign tumors are removed by more or less subtotal thyroidectomy. Differentiated carcinoma and undifferentiated carcinoma both indicate near-total thyroidectomy. Surgery is followed by 131I scan, 131I uptake, chest x-ray, and a measurement of serum thyroglobulin (TG) level as appropriate, for the patients with differentiated carcinoma. Serum TG, bone scan, and chest x-ray are used for those with undifferentiated carcinoma. Depending upon the results of the above tests, treatments are selected from the following: external radiotherapy, injections of 30-50 mCi 131I, chemotherapy, and administration of thyroxine or tri-iodothyronine. (57 Refs)

25. THE DIAGNOSIS OF MALIGNANCY IN DYSHORMONOGENETIC GOITRE.

Vickery AL
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Clin Endocrinol Metab; 10(2):317-335 1981

A review is presented of the pathology of dyshormogenetic goiters, which are known by several terms, including dyshormogenetic goiter, congenital goiter, familial goiter, familial goitrous cretinism, sporadic hypothryroidism, and sporadic goitrous cretinism. Subnormal production of thyroid hormone and increased thyroid-stimulating hormone (TSH) are associated with an asymmetric multinodular gland which appears microscopically as 'intense hyperplasia.' Histological diagnosis of malignancy is difficult and pathologists vary in their interpretations of the same specimens. The linkage of elevated TSH to the development of malignancy in dyshormogenetic goiter remains a matter for speculation. (39 Refs)

26. IODINE-123 FOR PEDIATRIC THYROID STUDIES: AN EVALUATION OF ITS ROLE.

Gulenchyn KY, Brown RG, Green MD, Ash JM
Div. Nuclear Medicine, Dept. Radiology, Hosp. Sick Children, Toronto, Canada
J Radioanal Chem; 65(1/2):251-257 1981

The use of 123I for thyroid studies was evaluated in 17 children (newborn to 15 yr old). Sixteen thyroid scans were performed; two whole-body scans (WBS) were performed to detect metastases of thyroid carcinoma. One patient had two scans performed at a 1-yr interval. A dose of 150-1,000 uCi 123I was administered po according to body surface area. The only radionuclide contaminant in the 123I was 125I. Scans were made approx 24 hr after administration of 123I and utilized a pinhole collimator with a 0.5 or 1.0 cm aperture. Eight thyroid scans indicated normal thyroid function. Eight abnormal cases included one with a solitary palpable nodule who was receiving thyroxine, five with thyroiditis, and two with lingual thyroids. One WBS indicated lymphatic metastases, but did not detect hepatic metastases shown by 99mTc scans. The second WBS showed no abnormality except remnants of thyroid tissue. From the results a pediatric dose range of 250-750 uCi is recommended. Reduction of scanning time without loss of resolution requires increasing the dose of 123I. Initial screening with 99mTc is recommended; 123I scans are recommended in cases where 99mTc cannot provide adequate information and for WBS. (11 Refs)

27. THE DIFFERENTIAL DIAGNOSIS OF HYPERCALCITONINISM.

Dambacher MA, Born W, Heitz PU, Olah AJ, Tobler PH, Fischer JA
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Schweiz Med Wochenschr; 111(49):1897-1901 1981

Plasma levels of calcitonin (CT) are highest in patients with medullary thyroid carcinoma (MTC). Plasma CT is also raised in some patients with carcinoma such as that of the breast, the lung or the pancreas, and in pheochromocytoma. It must be kept in mind, however, that plasma CT can be similarly raised in patients with renal failure, non-tumoral pulmonary disease or acute pancreatitis. In hypercalcemic patients with primary hyperparathyroidism the plasma CT is normal or only marginally elevated. It is speculated that the raised levels in pregnant and lactating women and in new-born infants prevent excessive bone destruction at times of greater physiological need for calcium. Larger mol wt forms than monomeric CT-(1-32) are circulating at least in plasma of patients with calcitonin-producing tumors and in renal insufficiency. The biological function of these larger molecular wt forms is not yet known. The discrepancies among the results of different laboratories can in part be explained by the immunoheterogeneity of the hormone and the different antigenic recognition sites of the antisera used. The measurement of plasma CT levels is nevertheless important for the diagnosis of MTC and may prove useful in some patients with malignant tumors unrelated to the C-cells of the thyroid gland. CT-radioimmunoassay may be improved by using antibodies specific to the different forms of circulating calcitonin. (Author abstract) (16 Refs) (In GER)

28. FOLLOW-UP OF PATIENTS WITH CANCER OF THYROID C-CELLS. RESULTS OF CALCITONIN DETERMINATIONS FOLLOWING SELECTIVE VENOUS CATHETERIZATION.

Reiners C, Schramm A
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MMW; 123(45):1708-1710 1981

Calcitonin levels were determined in blood samples obtained by selective venous catheterization from four patients with clinical evidence of metastases or recurrence of cancer of calcitonin-producing cells (C-cells) of the thyroid. In two patients, the tentative diagnoses were confirmed and the locations of the metastases were estimated. In the remaining two patients, the results of the calcitonin determinations were negative, but the tentative diagnoses were subsequently confirmed cytologically or histologically. (25 Refs) (In GER)

29. FAMILIAL MEDULLARY THYROID CARCINOMA AND C CELL HYPERPLASIA.

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Clin Endocrinol Metab; 10(2):351-365 1981

Normal C cells are clearly identified by their positive calcitonin test when cal citonin antisera and immunofluorescent or immunoperoxidase techniques are used. Medullary thyroid carcinoma are rich in calcitonin. In a study of the J kindred, including four generations and 83 family members, 12 members had calcitonin levels which could be elevated to greater than 2.0 nanog/ml upon stimulation and had bilateral medullary thyroid carcinoma located in the middle third of the lateral lobes--the site of greatest C cell density in normal glands. None of the patients had exhibited physical abnormalities before total thyroidectomy was undertaken. In a 9-yr study involving the J kindred, annual calcium gluconate infusion or pentagastrin injection used to detect calcitonin secretory reserve yielded a total of 21 patients in the group who converted from normal to abnormal levels. Except for one false negative, all glands resected from these patients showed bilateral C cell abnormalities ranging from hyperplasia to microscopic carcinoma. A hypothesis for familial medullary thyroid carcinoma proposes an increase in number and size of C cells with progression until C cell hyperplasia breaks through the basement membrane of the thyroid interstitium. Calcitonin is an efficient marker for tumor cells and has allowed early detection of carcinomas previously detectable only after metastasis. C cell hyperplasia is thought to be a manifestation of a mutational event that is hereditary; a hypothetical second mutational event leads to neoplasia. All members of a family in which familial disposition to medullary thyroid carcinoma has been established by histopathological detection of C cell hyperplasia should be screened annually for abnormalities of calcitonin secretory response, and for abnormalities of adrenal medullary and parathyroid functioning. Surgery should follow when tests are positive. (46 Refs)

30. RENAL LITHIASIS AND HYPERPARATHYROIDISM: DIAGNOSIS, MANAGEMENT AND PROGNOSIS.

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J Urol; 126(6):720-722 1981

From 1969 to 1979, 448 patients underwent parathyroid exploration for presumed hyperparathyroidism. Of these patients 184 had associated renal calculus disease, 72 of whom (16%) had metabolically active stone disease. Of these 72 patients 48 had adenomas, 18 had hyperplasia and 6 had normal glands. Of those patients with assessable disease none with adenomas has had recurrent calculi, whereas calculi continued to form in 45% of the patients with hyperplastic glands and in 50% of those with normal glands. Although most patients with adenomas had persistent calcium elevations 13 were identified with only intermittent hypercalcemia. Serum parathormone served to confirm the presence of parathyroid pathology. Urinary calcium levels were of no diagnostic benefit. (Author abstract) (15 Refs)

31. PERCUTANEOUS TRANSHEPATIC PORTAL VEIN CATHETERIZATION IN THE DIAGNOSIS OF HORMONE-PRODUCING TUMORS IN THE SPLANCHNIC AREA.

Luska G, Zick R, Otten G, Mitzkat HJ

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ROEFO; 135(5):566-571 1981

During 1980, percutaneous transhepatic portal vein catheterization was carried out in eight patients with suspected hormone-producing tumors in an attempt to localize these. Seven patients with hyperinsulinism were suspected of having an insulinoma and one a gastrinoma. There were no complications following the catheterization, and difficulties were reduced by the use of a special catheter. The blood samples were examined by radio-immunological methods for insulin or gastrin. On the basis of localized rise in hormone level, it was possible to diagnose three insulinomas and one gastrinoma in the pancreas. The beta-cell tumors were removed by enucleation or segmental resection, the gastrinoma by a Whipple's operation. Three patients showed an insulin gradient and sub-total pancreatectomies were performed. In one patient there was no definite abnormality in the insulin level and an operation has so far not been performed. Our experience indicates that this technique is difficult, but is nevertheless a reliable method for localizing hormone-producing tumors and surgery should not be carried out without it. (Author abstract) (31 Refs) (In GER)

32. CLINICAL COURSE OF CHORIOCARCINOMA AND RESULTS OF TREATMENT OF CHORIOCARCINOMA.

Maruo T, Tojo S, Ashitaka Y, Harada A

Dept. Obstetrics and Gynecology, Kobe Univ. Sch. Medicine, Kobe, Japan

Nippon Gan Chiryo Gakkai Shi; 16(4):704-712 1981

Effects of chemotherapy and surgery were studied in 29 women with choriocarcinoma. Metastatic lesions were observed in 23/29; 22/29 had lung metastases, 10/29 had brain metastases, 5/29 had vaginal metastases, and 4/29 had kidney metastases. One course of combination chemotherapy consisted of methotrexate (15 mg/day x 7 days), actinomycin D (0.5 mg/day x 5 days), adriamycin (10 mg/day x 5 days), and vinblastine (10 mg/day, 1x/wk). Av pretreatment levels of human chorionic gonadotropin (hCG) were 21,300 IU/liter in 6/29 patients who did not have involvement of cancer outside the uterus; all six had complete remission following hysterectomy and an av of 1.5 courses of chemotherapy. Av pretreatment levels of hCG were 70,700 IU/liter in nine patients who had only lung metastases; 7/9 had remission following hysterectomy and an av of 5.5 courses of chemotherapy. Av pretreatment levels of hCG were 211,500 IU/liter in nine patients with metastases to the lung and other organs; 1/9 had remission following surgery and 13 courses of chemotherapy, and 8/9 died within 3 mo of treatment. Av pretreatment levels of hCG were 197 IU/liter in three patients with lung or brain choriocarcinoma and without evidence of uterine lesions; all three had remission, but two had recurrence thereafter. Levels of hCG were thought to have clinical significance as markers of prognosis in patients with choriocarcinoma; follow-up of patients for 2 yr after remission was thought to be important. (12 Refs) (In JPN)

33. THE USE OF TAMOXIFEN IN GESTATIONAL TROPHOBLASTIC DISEASE (MEETING ABSTRACT).

Murray JC, Tattersall M
Women's Hospital, Crown Street, Sydney, Australia
Obstetrics and Gynaecology: 8th Asian Congress, October 25-31, 1981, Melbourne, Australia. Asia and Oceania Federation of Obstetricians and Gynaecologists 352 pp., 1981.

Eight women with proven gestational trophoblastic disease were treated with the anti-estrogen Tamoxifen following three serum beta human chorionic gonadotropin (HCG) titers, two wk apart, which had plateaued. In six of the eight patients there was a very rapid fall in beta HCG titer to biochemical zero. In the remaining patients there was a continuing fall but not at such a rapid rate. It would appear that Tamoxifen does have a place in the management of seemingly benign gestational trophoblastic disease in accelerating beta HCG falls, especially where the residual tumor mass is small. (no Refs)

34. ELEVATED PLATELET NOREPINEPHRINE CONCENTRATION IN PATIENTS WITH PHEOCHROMOCYTOMAS.

Feldman JM, Klatt C
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Clin Chim Acta; 117(3):279-288 1981

Concentrations of plasma and platelet norepinephrine were determined in simultaneously drawn blood samples from six patients with pheochromocytomas. A radioenzymatic method was used which employs the enzyme phenylethanolamine-N-methyltransferase to convert the norepinephrine to radioactive epinephrine. All patients had elevated platelet norepinephrine concentrations in the preoperative or intraoperative period. The plasma norepinephrine concentration was found in 3/6 patients. Platelet and plasma norepinephrine of five patients returned to normal after resection of benign pheochromocytomas. The platelet and plasma norepinephrine concentration of a patient with a malignant, non-resectable pheochromocytoma remained elevated. Elevated platelet norepinephrine concentrations were noted in 8/30 patients with hypertension, not thought to be due to pheochromocytoma. Diastolic blood pressures of these patients were 120 mm Hg or greater at the time the blood samples were drawn. Patients with pheochromocytomas had elevated platelet norepinephrine concentrations while normotensive. Only 5/60 patients without a history of hypertension had elevated platelet norepinephrine concentrations. Platelet norepinephrine determination is a good screening test for patients with a history of hypertension 'spells', for pheochromocytomas. An elevated value should be followed up with measurements of vanillylmandelic acid and catecholamines in a 24-hr urine collection. (16 Refs)

35. THE CLINICAL LABORATORY DIAGNOSIS OF NEUROBLASTOMA AND PHEOCHROMOCYTOMA.

Kincaid HL
Children's Hosp. Natl. Medical Center, Washington, DC
Clin Proc Child Hosp Natl Med Cent; 37(6):368-376 1981

Clinical application of assay techniques for measuring catecholamines to the detection of neuroblastoma and pheochromocytoma in children is discussed. The higher concentrations of catecholamines in pheochromocytomas indicated that tumor tyrosine hydroxylase is less sensitive to product inhibition than that in the normal tissue. Human neuroblastoma cells were found to contain the enzymes required for catecholamine synthesis, but the relative absence of storage granules was shown to result in rapid degradation of the newly synthesized epinephrine (E) and norepinephrine (NE) to vanilmandelic acid (VMA), as well as in the increase of dopamine (DA) production. The use of high performance liquid chromatography (HPLC) and radioenzymatic assay (REA) provides for an increased detection rate of catecholamines and a variety of metabolic intermediates. HPLC separates E, NE, and DA. The REA approach also offers improved sensitivity and specificity compared with fluorometric assays. (15 Refs)

36. PHENYLETHANOLAMINE-N-METHYLTRANSFERASE ACTIVITY DETERMINES THE EPINEPHRINE CONCENTRATION OF PHEOCHROMOCYTOMAS.

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Res Commun Chem Pathol Pharmacol; 34(3):389-398 1981

We evaluated the activity of phenylethanolamine-N-methyltransferase (PNMT) and dopamine-beta-hydroxylase (DBH) in 16 pheochromocytomas. Ten of the tumors were from patients with Multiple Endocrine Neoplasia and six of the tumors were from patients with sporadic pheochromocytomas. All of the pheochromocytomas contained PNMT and DBH activity. There was a significant correlation between PNMT activity and epinephrine concentration in the pheochromocytomas ($r = 0.61$); there was no significant correlation between PNMT activity and norepinephrine concentration ($r = 0.38$) or DBH activity and norepinephrine ($r = 0.06$) or dopamine ($r = 0.31$) concentration. In general, the patients with the highest PNMT activity in their pheochromocytomas tended to have paroxysmal (rather than sustained) hypertension and to excrete more E than NE in their urine. (Author abstract) (21 Refs)

37. SERUM ERYTHROPOIETIN (ESF) TITERS IN POLYCYTHEMIA.

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Blood; 58(6):1171-1174 1981

Serum ESF titers were measured in 42 polycythemic patients using the fetal mouse liver cell bioassay. ESF titers in patients with secondary polycythemia differed significantly from those in patients with polycythemia vera (p less than 0.00001). Among the 21 patients with secondary polycythemia, 1 patient had an ESF titer less than 10 mU/ml (the lower limit of sensitivty) and 20 had ESF titers that ranged between 11 and 112 mU/ml, with a mean titer of 56 mU/ml. Among the 21 patients with polycythemia vera, 13 patients had ESF titers less than 10 mU/ml and 8 had ESF titers ranging between 12 and 55 mU/ml, with a mean titer of 26 mU/ml. The mean hemoglobin concentration in the 8 patients with ESF titers greater than 10 mU/ml was significantly below that in the 13 polycythemia vera patients with ESF titers less than 10 mU/ml (p less than 0.03). If ESF titers less than 10 mU/ml had been indicative of polycythemia vera and ESF titers greater than 10 mU/ml had been indicative of secondary polycythemia in patients with hemoglobin concentrations greater than 17.7 g/dl, but not indicative of either condition in patients with hemoglobin concentrations less than 17.7 g/dl, 71.5% of the polycythemic patients in this study would have been diagnosed correctly, 9.5% incorrectly, and in 19% the diagnosis would have remained uncertain. It was concluded that measurement of serum ESF titers using this in vitro bioassay can be of clinical importance in differentiating between polycythemia vera and secondary polycythemia. (Author abstract) (22 Refs)

EFFECTS ON NORMAL AND NEOPLASTIC CELLS AND TISSUES

38. EVIDENCE THAT THYROTROPIN-RELEASING HORMONE TRANSIENTLY DECREASES MEMBRANE POTENTIAL IN MOUSE PITUITARY THYROTROPIC TUMOR CELLS IN CULTURE AS MONITORED BY TRIPHENYLMETHYLPHOSPHONIUM ION.

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J Biol Chem; 256(23):12445-12448 1981

The effect of thyrotropin-releasing hormone (TRH) on membrane polarization of mouse pituitary thyrotropic tumor (TtT) cells was measured indirectly using the lipophilic cation triphenylmethylphosphonium ion (TPMP+). The steady state level of TPMP+ accumulation was shown to be a linear function of the log of the extracellular K+ concentration between 4.5 and 75 mM and of TPMP+ concentration between 100 and 1,000 uM. The effect of increasing extracellular K+ on the accumulation of TPMP+ at equilibrium provides strong evidence that TPMP+ monitors membrane polarization in TtT cells since the membrane potential of anterior pituitary cells is largely dependent on a K+ diffusion gradient. The resting membrane potential of cells incubated with 4.5 mM K+, calculated from the Nernst equation, was-33 +-0.8 mV. TRH caused a loss of accumulated TPMP+ followed by its reaccumulation which was not due to a change in intracellular vol. The effect of TRH on TPMP+ accumulation was decreased in magnitude and in duration when TtT cells were incu bated in 50 mM K+. TRH caused a dose-dependent decrease in TPMP+ accumulation after 3.5 min; half-max loss occurred at approx 10 nM TRH. TRH had no effect on TPMP+ accumulation by GH3 cells, a clonal strain of rat pituitary cells that produce prolactin, when studied in parallel in medium with either 4.5 or 50 mM K+. During perfusion, TRH increased [3H]TPMP+ and 45Ca++ effluxes and thyrotropin release from TtT cells. These data provide evidence that TRH transiently decreases the mean polarization of TtT cells. We suggest that the decrease in polarization in TtT cells caused by TRH may be associated with Ca++ influx and serve to couple stimulation to thyrotropin release. This finding for TRH action in TtT cells is different than for GH3 in which TRH did not affect the mean membrane polarization. (Author abstract) (18 Refs)

39. HORMONE REGULATION OF DNA SYNTHESIS OF NORMAL AND HYPERPLASTIC HUMAN BREAST TISSUES IN VITRO AND IN VIVO (MEETING ABSTRACT).

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International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy Italian Society of Endocrinology; :A3 1981

The hormones analyzed in these studies were bovine insulin (5.0 ug/ml), ovine prolactin (5.0 ug/ml), human prolactin (5.0 ug/ml), human placental lactogen (5.0 ug/ml), human growth hormone (5.0 ug/ml), 17beta-estradiol (0.001 ug/ml) and progesterone (1.0 ug/ml). Epithelial (ductal) DNA synthesis of the cultured human breast tissues was significantly stimulated by insulin, human prolactin, human placental lactogen and 17beta-estradiol; ovine prolactin, human growth hormone and progesterone were without a stimulatory effect. The original morphology of the explants was maintained. In vivo studies (athymic nude mice): Human breast tissue was obtained and processed as described above and transplanted sc (dorsal) to 8 wk old female athymic nude mice (Balb/c). Thirty days after transplantation, the mice were treated with the following hormones: human placental lactogen (0.5 mg; 2 x daily); estrogen (17beta-estradiol, 1.0 ug, 1 x daily and estrone in drinking water, 0.5 mg/liter) or a sc grafted rat pituitary tumor (RPT) which secretes copious quantities of prolactin and growth hormone (host mice blood rat prolactin levels, greater than 4000 ng/ml). After 30 days of hormone treatment, the grafted human breast tissues were excised and incubated for 4 hr in a 3H-thymidine enriched culture media. The grafts were processed for 3H-thymidine autoradiography. Human placental lactogen, estrogen and estrogen + RPT significantly stimulated DNA synthesis of the ductal epithelium of the grafted human breast tissues; RPT alone was ineffective. One hundred percent of the grafts were accepted by control or hormone treated mice; no sign of immunological rejec tion was observed. The grafts acquired the host blood supply and retained the original morphology. The relative merits of our in vitro and in vivo systems for the study of human breast tissues will be discussed. (no Refs)

40. HORMONE LEVELS IN HUMAN BREAST CYST FLUID (RELATIVE PLASMA CYST FLUID LEVELS) AND STUDIES ON THE MECHANISM OF ENTRY OF HORMONES INTO BREAST CYSTS (MEETING ABSTRACT).

Bradlow HL, Schwartz MK, Fleischer M, Rosenfeld SS, Kream J, Breed CN, Fracchia AA
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International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy Italian Society of Endocrinology; :A4 1981

Cyst breast disease is a common occurence in women from age 35 to menopause. Although breast cysts are not precancerous per se, repeated studies over many yr have reported an increased risk for breast cancer in women with breast cysts when compared to normal controls. As part of a program to explore the possible relationship between the unusual hormone levels found in breast cyst fluid and the incidence of breast cancer, the concentration of a wide variety of hormones in breast cyst fluid were determined and compared with the plasma levels of these same compounds. Hormone levels were measured in cyst fluid from 1046 women who were then followed to determine breast cancer incidence. Both peptide and steroid hormones were measured in cyst fluid and in blood samples obtained simultaneously. The peptide hormones measured were luteinizing hormone (LH), follicle stimulating hormone (FSH), human prolactin (HPrL) and beta human chorionic gonadotropin (beta HCG). The first two compounds were present in cyst fluid in concentrations at or below plasma concentrations. HPrL and betaHCG however, were present in cyst fluid at concentrations greater than the plasma concentration in most of the patients studied. The cyst/plasma ratio ranged from only slightly greater than 1 to 200-fold. No correlation was found between the magnitude of the HPrL level and the betaHCG levels. The steroids studied were cortisol (F), testosterone (T), dihydrotestosterone (DHT), progesterone (P), estradiol (E2), estrone (E2), dehydroisoandrosterone (D), androsterone (A), and the sulfates of the latter four compounds. F, T, P. DHT, E1 and E2 were not significantly elevated in cyst fluid over plasma levels. D, A, DS, AS, E1S and E2S all showed elevated cyst fluid/plasma ratios, indeed in some cases as much as several thousand-fold greater than . Levels of DS and AS were as high as 20000 ug/dl. E1S and E2S were also markedly elevated in cyst fluid. (no Refs)

41. NEUROHORMONAL AND CHEMOSENSITIVITY OF HUMAN MELANOMA COLONY FORMING UNITS IN SOFT AGAR (MEETING ABSTRACT).

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Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, B russels, Belgium European Organization for Research on Treatment of Cancer; :A20 1981

We measured the effect of a series of non-steroidal hormones (follicle stimulating hormone (FSH), luteinizing hormone (LH), melanocyte stimulating hormone (MSH), human chorionic gonadotropin (HCG), melatonin, nerve growth factor (NGF)) on human melanoma colony forming cells in soft agar from biopsies of 20 patients with metastatic melanoma. A complex array of responses were demonstrated, suggesting that a diversity of hormonal phenotypes are present. Melanoma colony forming units in soft agar from biopsies of 50 patients with metastatic melanoma demonstrated marked heterogeneity in chemosensitivity to nine chemotherapeutic drugs. Reduction in survival of colony forming units below 38% at one-tenth the pharmacologically achievable one hr concentration x time (our operational definition of chemosensitivity) was obtained in only 19% of 200 in vitro trials and was generally identical whether patients had been exposed to prior chemotherapy or not, suggesting that melanoma colony forming units are inherently resistant to presently available chemotherapeutic drugs. The soft agar assay was 86% accurate (25 of 29 cases) for identifying drugs to which the tumor was resistant in vivo and 63% accurate (12 or 19 trials) for identifying drugs to which the tumor was clinically sensitive when mixed responses were included as responses. In contrast, if mixed responses were classified as progressive disease, then the accuracy for identifying sensitivity fell to 42% (8 of 19 trials). These investigations furnish a quantitative description of the chemosensitivity of human metastatic melanoma colony forming units and demonstrate that neurohormones can modulate melanoma colony forming units. Additionally, these studies can be regarded as a useful step towards the development of an in vitro chemosensitivity test for human melanoma and provide an operational quantitative basis for further exploration of in vitro directed therapy in metastatic neoplasms and classification of melanoma by neurohormonal responses. (no Refs)

42. LUTEINIZING HORMONE-RELEASING FACTOR INCREASES RELEASE OF HUMAN CHORIONIC GONADOTROPHIN IN ISOLATED CELL COLUMNS OF NORMAL AND MALIGNANT TROPHOBLASTS.

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Int J Cancer; 29(1):9-11 1982

The effect of synthetic luteinizing hormone-releasing factor (LRF) on release of human chorionic gonadotrophin (hCG) was studied by isolated cell columns of normal syncytiotrophoblasts and choriocarcinoma (BeWo) cells. After LRF stimulation the release of hCG by the normal trophoblasts increased up to 4-fold and release by the malignant trophoblasts increased up to 6-fold, indicating a specific effect of LRF on normal and malignant trophoblast cells. (Author abstract) (9 Refs)

43. ALTERATIONS IN CALCITONIN AND PARATHYROID HORMONE RESPONSIVENESS OF ADENYLATE CYCLASE IN F9 EMBRYONAL CARCINOMA CELL TREATED WITH RETINOIC ACID AND DIBUTYRYL CYCLIC AMP.

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J Cell Physiol; 109(3):453-459 1981

Adenylate cyclase (AC) was assayed by measuring conversion of (alpha-32P) ATP to cyclic (32P) AMP at 37 C in F9 embryonal carcinoma cells induced to differentiate to endodermal cells by exposure to 30 nanog/ml retinoic acid. Basal, guanosine triphosphate-, and fluoride-stimulated AC activities increased as induced change in cells occurred. The endodermal cell type showed little AC stimulation in response to calcitonin, and a strong increase in parathyroid hormone response. This behavior is the opposite of that in untreated F9 cells, which show greatest cyclic AMP stimulation with calcitonin, and little with parathyroid hormone. Treatment of retinoic acid-generated endodermal cells with dibutyryl cyclic AMP yields a type with neural-like morphology. AC in these cells was stimulated by parathyroid hormone, prostaglandin E1, isoproterenol, and epinephrine, but calcitonin response was lost. The possible metabolic role during development for calcitonin and parathyroid hormone indicated by these results implies that changes in AC hormonal responsiveness could serve as markers of early differentiation stages. (25 Refs)

44. ALKALINE PHOSPHATASE INHIBITION BY PARATHYROID HORMONE AND ISOPROTERENOL IN A CLONAL RAT OSTEOSARCOMA CELL LINE. POSSIBLE MEDIATION BY CYCLIC AMP.

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Calcif Tissue Int; 34(1):59-66 1982

The effect of parathyroid hormone (PTH 1-34 bovine) on alkaline phosphatase activity was investigated in an osteoblast-like clonal cell line derived from rat osteosarcoma (ROS 17/2). The properties of ROS 17/2 alkaline phosphatase resembled those of alkaline phosphatase from bone and from both human and mouse osteosarcoma cells. Levamisole inhibition and electrophoretic mobility resembled the rat bone enzyme activities. Incubation for 15 min at 56 C destroyed 98% of the alkaline phosphatase activity in butanol-extracted rat bone homogenate, and 85% of that in a similarly treated ROS 17/2 particulate fraction. The specific activity of ROS 17/2 alkaline phosphatase increased with time in culture. The increase was inhibited by PTH 1-34 and (-)-isoproterenol in a dose-dependent manner, starting at near-physiological hormone concentration (measured 48 hr after hormone addition). The ID50 values were 0.02 nano (n)M for PTH 1-34 and 1.7 nM for isoproterenol. The two hormones stimulated ROS 17/2 adenylate cyclase at higher concentrations: 13 nM for PTH 1-34 and 16 nM for isoproterenol. The rise in alkaline phosphatase was also inhibited by dibutyryl cyclic AMP and 8-bromo-cyclic AMP (0.1 milliM). Results suggest that PTH inhibition of alkaline phosphatase represents a physiological response to the hormone in the ROS 17/2 cell line; the findings implicate cyclic AMP as a mediator of the PTH effect. (43 Refs)

45. COMPARISON OF PATHOLOGICAL AND BIOCHEMICAL STUDIES OF TRANSPLANTED MORRIS HEPATOMAS.

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Howard Univ., Coll. Medicine, Washington, DC, 20059
Adv Enzyme Regul; 19:19-25 1981

Ten consecutive generations of each of 57 hepatoma cell lines, 5,000 transplantable tumors, have been monitored to define their salient morphologic features. Also the lungs of rats bearing these tumors were evaluated for evidence of transplantable tumor cellular metastases. These evaluations have led us to conclude the following. (a) The pattern of tumor cell growth is uniform and consistent from generation to generation. (b) Tumor cell pleomorphism is extremely variable. (c) All tumors are well vascularized. (d) Mitoses are variable between generations. (e) Varying amounts of necrosis are always present in all tumor cells lines. (f) The degree of differentiation is uniform in a given tumor line. (g) All well differentiated transplantable tumors metastasize to normal lungs but not to inflamed lungs. (h) Undifferentiated or poorly differentiated transplantable tumors cells rarely metastasize to the lungs. Four major program areas are reviewed. (a) Several of the Morris hepatomas may be hormone dependent or hormone responsive with regard to glucagon, insulin, cortisol or thyroxine. (b) The feedback regulatory control in cholesterol synthesis, which is missing in every Morris hepatoma, is probably located at the hydroxymethylglutaryl-CoA reductase site of action. (c) The intracellular 'second messenger' system in the hepatomas shows lost responsiveness of the cyclic AMP subsystem and increased responsiveness of the cyclic GMP subsystem. (d) The major factors in determining a tumor tissue's response to radiation and/or chemotherapy are cell doubling times, cell loss factors, cellular growth fractions, and cell cycle intervals. (Author abstract) (28 Refs)

46. INSULIN-STIMULATED GLUCOSE UTILIZATION IN ADIPOSE TISSUE FROM RATS BEARING WALKER 256 CARCINOMA.

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Dept. Biochemistry, Kirksville Coll. Osteopathic Medicine, Kirksville, MO, 63501
Cancer Lett; 15(1):41-51 1982

Adipose tissue glucose utilization in response to insulin and plasma insulin level were compared in normal rats and rats bearing the Walker 256 carcinoma. Male Sprague-Dawley rats (125-150 g) were implanted im with Walker 256 carcinoma. After 10-14 days, tumor-bearing rats and control rats were killed. The ability to promote the in vitro utilization of glucose by epididymal adipose tissue was assessed. The sensitivity of free adipocytes and minced adipose tissue from tumor-bearing rats to insulin, assessed by measurement of the incorporation of glucose into total lipids and into the triglyceride fraction of neutral lipids, was significantly less as compared to control animals (+188.8 +-27.5% vs +24.3 +-12.9% increase). In vitro insulin-stimulated glycogenesis in adipose tissue from control and tumor-bearing rats was significantly more effective in the control animals than in the tumor-bearing (+127.7 +-18.9% vs +42.4 +-9.7%). Adipose tissue from tumor-bearing animals tended to convert less glucose to CO2 in the presence of insulin than did adipose tissue from controls. Serum glucose levels were also lower in tumor-bearing rats than in corresponding control animals. The presence of the tumor resulted in lower circulating insulin in the tumor-bearing animals. The decreased in vitro sensitivity to insulin of adipose tissue from tumor-bearing animals is not the result of down-regulation by high levels of circulating insulin. (33 Refs)

47. DIFFERENCE BETWEEN MAGNESIUM AND MANGANESE IONS IN MODIFICATION OF EFFECT OF CATECHOLAMINE ON ADENYLATE CYCLASE SYSTEM IN EHRLICH ASCITES TUMOR CELLS.

Kurokawa T, Kitamura Y, Moriuchi M, Ishibashi S
Dept Physiological Chemistry, Inst. Pharmaceutical Sciences, Hiroshima Univ. Sch. Medicine, Minami-ku, Hiroshima 734, Japan
J Pharmacobio Dyn; 4(10):794-797 1981

Basal and norepinephrine-stimulated adenylate-cyclase activities in Ehrlich ascites tumor cells were measured in the presence of various concentrations of either Mg++ or Mn++. Both activities increased gradually with increase in Mg++ concentration. Both activities were max in the presence of low Mn++ concentrations, and decreased with increase in concentration. The decrease in activity was more pronounced in the norepinephrine-stimulated activity. Similar difference between the two divalent cations was observed in the effect on binding of the beta-adrenergic ligand to the membrane receptor. (13 Refs)

48. EFFECTS OF VASOPRESSIN, NORADRENALIN AND OXYTOCIN ON BLOOD FLOW DISTRIBUTION IN RAT KIDNEY WITH NEOPLASM.

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Acta Radiol Oncol Radiat Phys Biol; 20(4):253-260 1981

The arterial blood flow distribution between tumor and intact renal tissue was investigated in rats with transplanted sarcomas. Changes in tissue flow were measured by the microsphere tracer technique, and the redistributing effects on blood flow of vasopressin, noradrenalin and oxytocin was recorded. Bolus injections of vasopressin gave a transient decrease of intact tissue flow, not found in tumors. At increasing doses of vasopressin and in early tumor growth phase, the flow discriminating effect tended to vanish. Constant intravenous infusion of vasopressin gave similar reduction of flow in tumor and intact Tissue. Selective administration into the renal artery reduced flow in intact tissue but produced ambiguous effects in tumor tissue. Noradrenalin produced less reduction of tumor flow as compared with intact tissue flow. Oxytocin increased tumor blood flow while no flow change occurred in intact tissue. Oxytocin thus appeared to produce the most favorable redistribution of flow within tumor kidneys for the prospect of conveying cytotoxic agents selectively to the tumor. (Author abstract) (24 Refs)

49. INFLUENCE OF HISTAMINE AND SEROTONIN ANTAGONISTS ON THE GROWTH OF XENOGRAFTED HUMAN COLORECTAL TUMORS.

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JNCI; 67(6):1207-1212 1981

Four lines of human colorectal cancer were established and serially propagated as subcutaneous xenografts in immunosuppressed inbred CBA/Lac mice. Established xenografts were then used to investigate the influence of a serotonin antagonist (BW 501c) and a histamine H2 receptor antagonist (Cimetidine) on xenograft growth. The growth of each of the four tumor lines was significantly inhibited by BW 501c throughout the treatment, whereas the growth of only two tumor lines was significantly inhibited by Cimetidine treatment. The response of individual tumor lines was not predictable on the basis of either tumor histopathology or the natural growth rate of the untreated xenograft. A number of alternative, but not mutually exclusive, hypothesis are suggested to explain the results. One hypothesis proposes that colorectal tumors are composed of subpopulations of tumor cells that are variously dependent on or independent of amine hormones. Another hypothesis is that tumor cells exhibit temporal changes in hormone sensitivity to amine hormones during treatment. Finally, it is suggested that serotonin and/or histamine H2 antagonists may be useful in preventing the repopulation of colorectal carcinomas following antineoplastic therapy with the use of conventional drugs. (Author abstract) (10 Refs)

50. EFFECT OF 12-O-TETRADECANOYL-PHORBOL-13-ACETATE ON CA2+ EFFLUX AND PROTEIN DISCHARGE IN PANCREATIC ACINI.

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J Biol Chem; 256(23):12040-12045 1981

When pancreatic acini are exposed to the peptide cerulein (an analogue of the hormone cholecystokinin) or the cholinergic agonist carbamylcholine, they exhibit a rapid release of intracellular Ca++ and a rise in the level of cGMP, accompanied by discharge of secretory proteins. The phorbol ester 12-O-tetradecanoyl-phorbol-13-acetate (TPA) stimulates protein discharge without affecting the level of cGMP, while N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) elevates cGMP, but does not elicit discharge. To clarify the relationships among these events, the effect of TPA and MNNG on Ca++ efflux in guinea pig acini was determined. Cells were incubated in medium containing 45Ca++ and transferred to medium with nonradioactive Ca++ before adding the agents to be tested. Cerulein (10(-9) M), carbamylcholine (10(-5) M), and the Ca++ ionophore A23187 (5 ug/ml) all caused the release of 40-60% of the cell-associated 45Ca++ within 3 min. In contrast, acini incubated with 10(-7) M TPA, 10(-4) M MNNG, or no added agents retained over 80% of their 45Ca++ after 22 min. TPA caused significant secretory discharge within the first 15 min and did not block Ca++ efflux stimulated by other secretagogues. TPA-induced discharge requires energy and the presence of sufficient Ca++ in the extracellular medium. These observations are consistent with a model in which the rapid release of Ca++ into the cytoplasm triggers an increase in the level of cGMP and, by a separate series of events, protein discharge. TPA may act at a later point on the pathway to discharge, but before an obligatory step requiring Ca++. (Author abstract) (31 Refs)

51. INTERACTION OF VASOACTIVE INTESTINAL PEPTIDE WITH HELA CELLS: ACTIVATION OF CYCLIC AMP-DEPENDENT PROTEIN KINASE AND LACK OF EFFECT ON DNA SYNTHESIS.

Prieto JC, Pintado E, De Miguel C, Guerrero JM, Goberna R
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Biochem Biophys Res Commun; 103(3):799-805 1981

Protein kinase activity stimulated by vasoactive intestinal peptide (VIP) was studied in HeLa cells. Max activation required the simultaneous presence of a phosphodiesterase inhibitor. The response was dose dependent and in accordance with the concentration of VIP required for half-max stimulation of cyclic AMP production. Secretin stimulation of protein kinase and stimulation of DNA synthesis were also studied. (18 Refs)

52. PLURIPOTENT HEMOPOIETIC PROGENITORS (CFU-GEMM) IN POLYCYTHEMIA VERA: ANALYSIS OF ERYTHROPOIETIN REQUIREMENT AND PROLIFERATIVE ACTIVITY.

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Blood; 58(6):1224-1227 1981

Pluripotent hemopoietic progenitors (CFU-GEMM) give rise to multilineage hemopoietic colonies in culture. We have examined the erythropoietin requirements of CFU-GEMM-derived erythroid progeny in patients with polycythemia vera (PV) and studied their proliferative activity by short-term exposure to 3HTdR. Mixed colonies with erythroid components were observed in all bone marrow and peripheral blood samples from patients with PV that were cultured without addition of exogenous erythropoietin. This response is consistent with previously reported growth patterns for CFU-E and BFU-E. The frequency of mixed colonies increased regularly when erythropoietin was added to the cultures. Short-term exposure of peripheral blood specimens to 3HTdR prior to plating yielded a reduction of the plating efficiency by 20%-70% when compared to cells that were not exposed to 3HTdR. The observation of cycling CFU-GEMM in PV contrasts with the usually quiescent behavior of CFU-GEMM in peripheral blood of normal individuals under steady-state conditions. These results support the view that the increased proliferative rate observed for CFU-GEMM may be responsible for the increased formation of blood cells in PV. (Author abstract) (19 Refs)

EFFECTS OF ENDOGENOUS AND EXOGENOUS AGENTS ON NON-STEROID HORMONE ACTIVITY

53. COMPARATIVE STUDY OF HUMAN FETAL, NORMAL ADULT, AND SOMATOTROPIC ADENOMA PITUITARY FUNCTION IN TISSUE CULTURE.

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J Clin Endocrinol Metab; 54(1):6-16 1981

Tissue from 14 somatotropic adenomas, 2 normal adult pituitaries, and 16 fetal pituitaries (10-20 weeks gestation) was maintained in culture for 2 weeks. The secretion of GH, PRL, LH, and TSH into culture medium was studied both in the basal state and in response to acute 3-hr exposure to TRH, apomorphine, somatostatin (SRIF), LRH, and theophylline. The findings were compared with results of in vivo dynamic pituitary function tests performed in the adult patients before transsphenoidal surgery. Several conclusions were reached (1) TRH may be a physiological regulator of GH secretion. Its paradoxical effect in acromegaly appears to be caused by an alteration at the level of the tumor cell. (2). The direct effect of apomorphine on normal pituitary tissue is a suppression of both GH and PRL secretion; the paradoxical GH suppression observed in vivo in some acromegalics is due to an alteration of the extrapituitary action(s) of apomorphine; on the other hand, nonresponsiveness of this dopaminergic agent seems to be caused by a change in the adenoma cell itself. (3) SRIF suppresses GH secretion from the normal pituitary and adenoma tissue in an identical manner. (4) The abnormalities observed in the adenomas generally do not appear to be a reversion toward the fetal state. (46 Refs)

54. ABNORMAL REGULATION OF PARATHYROID HORMONE RELEASE BY CALCIUM IN SECONDARY HYPERPARATHYROIDISM DUE TO CHRONIC RENAL FAILURE.

Brown EM, Wilson RE, Eastman RC, Pallotta J, Marynick SP
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J Clin Endocrinol Metab; 54(1):172-179 1981

Dispersed parathyroid cells were employed to study calcium-regulated parathyroid hormone (PTH) release in severe secondary hyperparathyroidism due to chronic renal insufficiency. Cell preparations were obtained from 16 parathyroid glands of six patients undergoing subtotal parathyroidectomy for parathyroid bone disease and/or hypercalcemia. The effects of increasing ambient calcium concentration on immunoreactive PTH release in vitro were assessed and compared with results observed in cells prepared from seven adenomas and six normal parathyroid glands. There was no difference in maximal PTH release for the three types of tissue (mean +- SEM, 8.48 +-1.9, 8.1 +-3, and 10.1 +-0.78 ng/10(5) cells/hr respectively). In 14 of 16 hyperplastic glands, 6 of 7 adenomas, and all of the normal glands, PTH release was inhibited more than 50% by 2-3 mM calcium (suppressible glands). Of the normal glands, half of the maximal inhibition of PTH release (the set-point) occurred at less than 1.03 mM calcium in five of six cases. In 12 of 14 suppressible hyperplastic glands and all of the 6 suppressible adenomas, on the other hand, the set-point was 1.03 mM or higher (p less than 0.01 and p less than 0.002, respectively). Thus, in severe secondary parathyroid hyperplasia due to chronic renal insufficiency, there is frequently an increase in the set-point for calcium without a change in the maximal secretory rate per cell. Abnormal calcium-regulated PTH release at the cellular level, therefore, is not limited to parathyroid neoplasia (ie adenoma of primary hyperplasia), but may occur in secondary hyperplasia as well. (Author abstract) (34 Refs)

55. CHANGES IN THYMUS FACTOR LEVEL IN RATS WITH JENSEN SARCOMA AND THE INFLUENCE OF APPLICATION OF THYMUS HORMONE ON TUMOR GROWTH RATE.

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Geschwulstklinik (Charite), Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany
Z Exp Chir; 14(5):306-309 1981

Changes in the plasma levels of thymus factor (TF) and the effects of various treatments were studied in Wistar rats bearing transplanted Jensen sarcomas. Adult rats (90-110 g) were injected in the thigh with 10(8) tumor cells. TF levels were determined 16 days after transplantation (TP). The following treatments were used singly or in various combinations: (1) Local irradiation (RT) was begun 2 days after TP with a total dose of 21 Gray (3 Gray/day for 5 days, 2 days pause, and 3 Grays/day for 2 days). (2) Cyclic AMP levels were raised by ip injection of l-dihydroxyphenylalanine (l-DOPA: 100 mg/kg, 3 x/day for 6 days, followed by 1 x or 2 x/day for 6 days). (3) Interferon production was induced by injection of measles vaccine (MV: 10,000 TCD50/day im on days 1, 3, and 5 after TP). (4) TF was injected ip (0.2 ml 2 x/day, for 12 days, beginning

1 day after TP). The lowest rate of tumor growth was obtained with a combination of RT, l-DOPA, and MV (11/13 rats tumor-free). All tumor-bearing animals showed lower plasma TF levels (107-119 units) than tumor-free animals (188-239 units). Animals responding to treatment had TF levels comparable to untreated, tumor-free controls. TF treatment alone and a combination of l-DOPA and MV reduced tumor growth significantly. (20 Refs) (In GER)

56. SOMATOSTATIN ELABORATION BY MONOLAYER CELL CULTURES DERIVED FROM TRANSPLANTABLE RAT MEDULLARY THYROID CARCINOMA: SYNERGISTIC STIMULATORY EFFECTS OF GLUCAGON AND CALCIUM.

Aron DC, Muszynski M, Birnbaum RS, Sabo SW, Roos BA
Endocrinology and Mineral Metabolism, Veterans Admin. Medical Center, Case Western Reserve Univ., 10701 East Boulevard, Cleveland, OH, 44106
Endocrinology; 109(6):1830-1834 1981

Somatostatin (SRIF)-producing transplantable rat medullary thyroid carcinomas (MTCs) were used to establish primary monolayer cell cultures for studying SRIF secretion and production. Immunoreactive SRIF (iSRIF) and calcitonin (iCT) levels in the MTC cell cultures were 252 and 4,900 ng/mg cell protein, respectively. The acute effects of calcium and glucagon on the elaboration of iSRIF and iCT were investigated in 3-hr experiments. Basal secretion rates (mean +- SE, five experiments) for iSRIF and for iCT were 10.7 +-2.5 and 297 +-33 ng/mg cell protein, respectively. Calcium stimulated the secretion of iSRIF and iCT in dose-dependent fashion. Maximal secretory effect of calcium was observed at 4-5 mM: iCT secretion increased 148% over basal, and iSRIF secretion increased 228% over basal. At 1 mM calcium, maximally effective doses of glucagon (1 uM) significantly increased iCT secretion (44% over basal) but not iSRIF secretion. At 5 mM calcium, as little as 10 nM glucagon had a significant stimulatory effect on secretion of both peptides. The largest stimulation was observed at 5 mM calcium and 1 uM glucagon; for iSRIF a 527% increase over basal and for iCT and 308% increase over basal were observed under this condition. At high calcium the stimulatory effect of glucagon on iSRIF secretion and on iCT secretion was significantly greater than at low calcium. In these 3-hr experiments neither 5 mM calcium nor 1 uM glucagon increased culture content (cells plus medium) of iCT or iSRIF. However, 3-hr treatment of the cell cultures with both agonists increased total culture content of iSRIF by 53% and iCT by 21%. The establishment of SRIF-producing cell cultures from transplantable rat MTCs and the identification of a synergistic secretagogue interaction for glucagon and calcium open the way for systematic in vitro investigation of SRIF secretion and biosynthesis. (Author abstract) (27 Refs)

RECEPTOR/ BINDING SITES

57. MAINTENANCE OF PROLACTIN RECEPTORS IN HUMAN BREAST CANCER.

Ben-David M, Dror Y, Biran S
Dept. Pharmacology, Hebrew Univ.-Hadassah Medical Sch., POB 1172, 91010 Jerusalem, Israel
Isr J Med Sci; 17(9/10):965-969 1981

Breast tissue specimens of 110 women with various stages of breast cancer were tested in vitro to determine their specific binding sites for human prolactin. In contrast to the case of steroid receptors, binding sites for prolactin were found in the vast majority of breast cancer tissue. Distribution profiles giving amount of prolactin receptor and their affinity coefficients were found to be similar in the tissues of women whose ages, hormonal status, or stage of breast cancer varied. These findings show that in contrast to steroid receptors, human breast cancer tissue maintains binding sites for prolactin. The findings also indicate that there may be a higher dependency of breast cancer on prolactin than on steroids. Clinical trials must be carried out to determine the role of 'positive' prolactin receptors in prognosis and prediction of response to future hormone therapy. (Author abstract) (20 Refs)

58. HUMAN PROLACTIN RECEPTOR AND DOPAMINE ACTIONS IN FEMINIZING ADRENAL NEOPLASTIC (FANG-8) CELLS (MEETING ABSTRACT).

Furuhashi N, Fang VS
Department of Obstetrics and Gynaecology, Tohoku University School of Medicine, Sendai, Japan
Obstetrics and Gynaecology: 8th Asian Congress, October 25-31, 1981, Melbourne, Australia. Asia and Oceania Federation of Obstetricians and Gynaecologists 352 pp., 1981.

With a clonal strain of human epithelial cells, derived from a feminizing adrenal neoplastic gland and designated Fang-8 cells, we have previously demonstrated that human prolactin (hPRL) stimulated the production of estrogen in the cell culture system. In these studies, the cell culture environment was kept at 37C, 5% CO2-95% air. To demonstrate the hPRL receptor in Fang-8 cells, we added 6-10 x 10(4) cpm of (125I-iodo-hPRL to 1 x 10(5) cells. The specific binding of hPRL receptor in Fang-8 cells was 2.85 + 0.94%. Drugs being tested were dopamine (10nM and 100nM), CB-154 (2-bromo-alpha - ergocryptine 0.6, 6, and 60 ug/dish), propranolol (1mM), phenoxybenzamine (1mM), primozide (1mM) and their combinations. At the end of the 24 hr incubation, the estrogen concentrations in each medium were measured by radioimmunoassay. Cell protein was measured by the method of Lowry et al. CB-154 produced stronger blocking action than dopamine. When alpha-, beta-adrenergic and dopaminergic blocking agents were tested, these blockers were inactive by themselves, the inhibitory effect of CB-154 on estrogen production being blocked only by propranolol (beta-adrenergic blocker). These data suggest the existence of an hPRL receptor in the Fang-8 cells. Dopamine and dopamine agonists inhibit estrogen production in Fang-8 cells by a mechanism not involving a prolactin receptor. (2 Refs)

59. EFFECT OF AN LHRH ANALOG ON GROWTH AND HORMONE RECEPTOR LEVELS IN DMBA-INDUCED MAMMARY TUMORS IN THE RAT.

Turcot-Lemay L, Cusan L, Seguin C, Kelly P, Labrie F
Dept. Molecular Endocrinology, Le Centre Hospitalier de l'Universite Laval, Quebec G1V 4G2, Canada
J Recept Res; 2(2):135-151 1981

Hormone-dependency of dimethylbenz(a)anthracene (DMBA)-induced mammary tumors in rats was studied. Daily injections of luteinizing hormone-releasing hormone (LHRH) agonist, [D-Ala(6), des-Gly-NH2(10)]LHRH ethylamide (LHRH-A), 1 ug/day, for 38 days resulted in a 35% decrease in the number of tumors present at the start of the experiment compared to decreases of 45% after ovariectomy and of 8% in the control group. Although LHRH-A administration resulted first in a stabilization in the number of tumors, a marked inhibitory effect of the LHRH agonist on total tumor mass/rat was observed. There was marked reduction in ovarian luteinizing hormone (LH) and follicle-stimulating hormone (FSH) receptors while prolactin receptors were unchanged. Estrogen and progesterone receptor levels decreased after ovariectomy but treatment with LHRH-A had no significant effect on these receptors. Plasma LH and FSH levels increased after ovariectomy. Treatment with LHRH-A was followed by similar but less marked increases in plasma LH and FSH, with significant decrease in plasma prolactin and progesterone levels. The mechanisms by which LHRH-A induces the antitumor effect probably is related to desensitization of the ovary to LH and FSH with a concomitant decrease in circulating levels of estrogen and prolactin. (21 Refs)

60. CALCITONIN INDUCTION OF A PERSISTENT ACTIVATED STATE OF ADENYLATE CYCLASE IN HUMAN BREAST CANCER CELLS (T 47D).

Lamp SJ, Findlay DM, Moseley JM, Martin TJ
(c/o Martin) Dept. Medicine, Univ. Melbourne, Repatriation General Hosp., Heidelberg, Victoria 3081, Australia
J Biol Chem; 256(23):12269-12274 1981

In a calcitonin-responsive human breast cancer cell line (T 47D), specific receptors exist for calcitonin in intact cells, which show saturable binding which is only slowly and incompletely reversible. Full stimulation of cyclic AMP production in the cells was achieved with less than 50% receptor occupancy. Pretreatment of cells in culture with calcitonin, followed by washing, led to loss of adenylate cyclase response to calcitonin in homogenates. This took place rapidly, reaching a maximum after 15 min of preincubation with 3 nM salmon calcitonin, and was associated with a substantial increase in basal adenylate cyclase activity, which was dose-dependent and agonist-specific, in that it did not occur upon treatment of the cells with prostaglandin E2. Receptor loss, as measured by decrement in specific binding of [125I]calcitonin to intact cells, took place more slowly, requiring at least 1 hr for completion. Recovery of adenylate cyclase responsiveness and return of basal activity to normal was a relatively slow process, always requiring more than 24 hr for completion. Neither the desensitization nor the persistent basal activity could be transferred in the cytosol compartment of calcitonin-preincubated cells. When calcitonin-preincubated cells were washed, and at intervals thereafter, the production of cyclic AMP was measured in the presence of a phosphodiesterase inhibitor, a 120-fold rise in basal cyclic AMP production was observed, and the response to added calcitonin was lost. Return of basal activity and of calcitonin responsiveness followed a time course similar to that seen in recovery of adenylate cyclase response. The results indicate the ability of calcitonin to induce rapidly a persistent state of adenylate cyclase activation which remains stable for several hours. This may be due to persistent tight binding of calcitonin but may also be related to changes induced by calcitonin in availability or function of nucleotide regulatory units. (Author abstract) (34 Refs)

61. COMPARISON OF THE IN VITRO EFFECT OF BIGUANIDES AND SULFONYLUREAS ON INSULIN BINDING TO ITS RECEPTORS IN TARGET CELLS.

Vigneri R, Pezzino V, Wong KY, Goldfine ID
Cattedra di Endocrinologia e Patologia Costituzionale, Universita di Catania, Ospedale Garibaldi, 95123 Catania, Italy
J Clin Endocrinol Metab; 54(1):95-100 1982

The in vitro effects of two biguanides (phenformin and metformin) and four sulfonylureas (tolbutamide, glyburide, gliclazide, and glisolamide) on insulin binding to its receptors were studied in four cultured cell lines: human skin fibroblasts, IM-9 lymphoblasts, MCF-7 human mammary carcinoma, and H35 rat hepatoma. After a 24-hr preincubation with maximal stimulatory concentrations of phenformin, specific [125I]insulin binding to its receptors in the four different cell lines was increased over control by 67.2 +-17.0%, 101.3 +-11.5%, 65.1 +-8.0 and , and 44.0 +-12.1%, respectively (mean +- SE). Phenformin was effective in IM-9 cells that were down-regulated by unlabeled insulin, and the effect of phenformin on insulin binding was not affected by inhibition of protein synthesis with cycloheximide. In concert with this observation, Scatchard plots indicated that phenformin increased the insulin receptor's affinity rather than the number of insulin-binding sites on IM-9 cells. Metformin was also effective in significantly enhancing insulin binding in both IM-9 and MCF-7 cells. In contrast to the effects of biguanides, none of the four sulfonylureas tested had any significant influence on insulin binding to any of the four cell lines. These agents were also ineffective in IM-9 cells that were down-regulated by insulin. Therefore, these studies suggest that: (1) in vitro, biguanides enhance insulin binding to its receptors in a variety of cell types; (2) this effect of biguanides doesn't depend on new receptor synthesis; it is a result of changes in the affinity of the insulin receptor; and (3) in contrast to the biguanides, the sulfonylureas do not have a major direct effect on insulin binding to its receptors in most cell types. (Author abstract) (19 Refs)

OTHER RELATED STUDIES

62. ENDOCRINOLOGICAL ASPECTS OF BREAST PHYSIOLOGY (MEETING ABSTRACT).

Robyn C
Human Reproduction Research Unit, Universite Libre de Bruxelles, Hopital Saint-Pierre, Brussels, Belgium
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy Italian Society of Endocrinology; :A2 1981

Growth of the mammary gland is discontinuous; a first wave occurs at puberty under the influence of sex steroids, and the parenchymal breast tissue differentiates into a ductular-lobular-alveolar system. Growth slowly continues with each menstrual cycle up to the age of 30-35. A second major wave of growth takes place during pregnancy. Estrogens, progesterone and prolactin with variable relative potencies induce proliferation and differentiation of alveolar epithelial stem cells and control arborization of the ductular-lobular system. The interplay of the three hormones seems to be essential for optimal and balanced growth of the mammary tissue. From mid-pregnancy, the secretory differentiation of the alveolar stem cells is induced, predominantly under the influence of prolactin in synergism with metabolic hormones: this involves Messenger (m)-RNA synthesis for the production of milk proteins and enzymes. However, during pregnancy most of the secretory effects of prolactin are suppressed and lactation does not occur: in vitro, progesterone suppresses the prolactin effects of casein m-RNA synthesis. After delivery, progesterone, estrogens and placental lactogen abruptly drop and prolactin induces full secretory activity and milk release. Oxytocin is required for milk ejection. Prolactin and oxytocin are released by neuroendocrine reflexes initiated by suckling. Prolactin does not appear to be essential for maintaining lactation. In mothers nursing for 2 yr or more, hyperprolactinemia persists for 15-18 mo; it is associated with infertility due to anovulation or corpus luteum deficiency. The decline in serum prolactin levels seen in the mothers after 18 mo of lactation is not associated with a decline in milk yield, at least when considering the amount of milk per feeding. Finally, the sequence of the endocrine events controlling full differentiation of the breast tissue and the timing of their occurrence seem to be of decisive importance in the resistance of the mammary epithelium to carcinogenic agents. (no Refs)

63. MECHANISMS OF BONE REMODELING INDUCED BY TUMORS: TUMOR HUMORS.

Tashjian AH
Lab. Toxicology, Harvard Sch. Public Health, Boston, MA, 02115
Schweiz Med Wochenschr; 111(49):1869-1872 1981

Mechanism of bone remodeling (BR) by tumor-induced alterations is reviewed. BR may be altered by the presence of metastatic tumor in bone, by the synthesis and release into circulation of humoral factors by tumor cells, or by syndromes with hypercalcemia. Cell culture and animal studies indicate that tumor cells secrete humoral factors, such as parathyroid hormone, which produce hypercalcemia. Animal studies with HSDM1 and VX2 tumors show that these tumors produce excessive amounts of prostaglandin E2 (PGE2), which stimulates bone resorption. PGE2 activity is inhibited by low concentrations of indomethacin (IM) or hydrocortisone (HC). IM and HC prevent or reverse hypercalcemia in tumor-bearing animals. High levels of PGE2 in veinous drainage of tumors indicates the tumors as the source of PGE2. The effects PGE2 are systemic and are not confined to the area of the tumor or metastases. Studies in mice show that epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) enhance metabolism of arachidonic acid, which can be metabolized to PGE2 by bone cells. EGF and PDGF may be produced by tumor cells. Understanding the effects of humoral factors on BR should facilitate proper therapy for tumor-related conditions. (38 Refs)

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CHARACTERIZATION OF NON-STEROID HORMONES IN EXPERIMENTAL AND IN VITRO SYSTEMS

1. HUMAN PITUITARY GONADOTROPIC ADENOMA; HISTOLOGICAL, IMMUNOCYTOCHEMICAL, AND ULTRASTRUCTURAL AND HORMONAL STUDIES IN EIGHT CASES.

Trouillas J, Girod C, Sassolas G, Claustrat B, Lheritier M, Dubois MP, Goutelle A
(c/o Girod) Laboratoire d'Histologie, Faculte de Medicine Alexis Carrel, Rue Guillaume Paradin, F-69372 Lyon Cedex 2, France
J Pathol; 135(4):315-336 1981

Histological, immunocytochemical, ultrastructural, and hormonal characteristics of human pituitary gonadotropic adenoma (PGA) were studied. In a series of 230 surgically removed

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pituitary adenomas, 8 had increased intratumor levels of gonadotropins and showed positive immunostaining for gonadotropic cells. Examination by light microscope showed all eight tumors to be composed of agranular cells that were generally PAS-negative. Immunofluorescent staining demonstrated immunoreactive follicle stimulating hormone (FSH) beta-subunits alone in two tumors, and FSH and luteinizing hormone (LH) in six tumors, of which two had immunoreactive FSH beta-subunits. Electron micrographs showed moderately or well developed endoplasmic reticulum that was frequently dilated. Also present were secretory granules of varying electron density and numerous microtubules. Hormonal analysis showed elevation of basal plasma levels FSH and LH in two cases and FSH alone in two cases. FSH and LH plasma levels were approx normal in three cases. Analysis of intratumor hormone levels showed elevated FSH and LH in five cases and FSH alone in two cases. Elevated FSH beta-endorphin was found in two cases. Other hormone levels were insignificant in all cases. Immunoreactivity of tumors correlated well with hormone levels in the tumors. Results suggest three types of PGA producing FSH alone, FSH and LH, or FSH, LH, or immunoreactive beta-endorphin. (56 Refs)

2. TWO DISTINCT INTRACELLULAR PATHWAYS TRANSPORT SECRETORY AND MEMBRANE GLYCOPROTEINS TO THE SURFACE OF PITUITARY TUMOR CELLS.

Gumbiner B, Kelly RB
Dept. Biochemistry and Biophysics, Univ. California, San Francisco, San Francisco, CA, 94143
Cell; 28(1):51-59 1982

The pituitary cell line, AtT-20, synthesizes adrenocorticotropic hormone (ACTH) as a glycoprotein precursor that is cleaved into mature hormones during packaging into secretory granules. The cells also produce an endogenous leukemia virus (MuLV) that is glycosylated after translation similar to the glycosylation of the ACTH precursor. Our evidence suggests that the envelope glycoprotein and some precursor ACTH get to the cell surface in a vesicle different from the mature ACTH secretory granule. Viral glycoproteins and ACTH precursor are released from the cells much sooner after synthesis than mature ACTH. Isolated secretory granules do not contain significant amounts of the envelope glycoprotein or ACTH precursor. Exposing cells to 8Br-cAMP stimulates release of mature ACTH four to five fold, but has little effect on the release of the ACTH precursor or the viral glycoproteins. We propose that the viral glycoproteins and some of the ACTH precursor are transported by a constitutive pathway, while mature ACTH is stored in secretory granules where its release is enhanced by stimulation. (Author abstract) (32 Refs)

3. GLYCOSYLATION STEPS INVOLVED IN PROCESSING OF PRO-CORTICOTROPIN-ENDORPHIN IN MOUSE PITUITARY TUMOR CELLS.

Herbert E, Phillips M, Budarf M
Dept. Chemistry, Univ. Oregon, Eugene, OR
Methods Cell Biol; 23:101-118 1981

Approaches to the study of proteolytic processing and glycosylation of the precu rsor in mouse pituitary tumor cells (line AtT-20/D16v) are outlined, including intermediate and end products of processing of pro-ACTH-endorphin, details of the glycosylation steps, use of the glycosylation inhibitor tunicamycin (TN) to determine if cleavage sites are specified by oligosaccharides, and structure of the ACTH-endorphin peptides from TN-treated cells. (58 Refs)

4. EVIDENCE FOR THE PRESENCE OF PRO-GAMMA-MELANOTROPIN, THE NH2-TERMINAL FRAGMENT OF THE CORTICOTROPIN-BETA-LIPOTROPIN PRECURSOR, IN CORTICOTROPIN-PRODUCING TUMOURS.

Alumets J, Ekman R, Hakanson R, Sundler F
(c/o Hakanson) Dept. Histology, Pharmacology and Nuclear Medicine, Univ. Lund, Solvegatan 10, S-223 62 Lund, Sweden
Virchows Arch [Pathol Anat]; 394(1/2):143-150 1981

Five corticotropin-producing tumors were examined for peptides related to the corticotropin-beta-lipotropin precursor. Two were basophil pituitary adenomas and three were bronchial carcinoids. The cells of the two pituitary adenomas stained with antisera against beta-endorphin and against pro-gamma-melanotropin, the NH2-terminal fragment of the corticotropin-beta-lipotropin precursor, but not with antisera against alpha-melanotropin or beta-lipotropin. The corticotropin-storing tumor cells of the bronchial carcinoids stained with antisera against beta-endorphin, beta-lipotropin or pro-gamma-melanotropin. Only one of the three bronchial carcinoids contained cells reacting with the antiserum against alpha-melanotropin. Although the two types of corticotropin-storing tumors (pituitary adenoma and bronchial carcinoid) differed with respect to beta-lipotropin content, the over-all picture indicates that the proteolytic processing of the corticotropin precursor proceeds along similar lines in tumor cells and in pituitary corticotrophs. An acetic acid extract of one of the bronchial tumors was subjected to gel chromatography and immunochemical analysis of material related to pro-gamma-melanotropin. The immunoreactive material displayed a considerable size heterogeneity, with the predominant components having a mol wt larger than that of authentic pro-gamma-melanotropin. (Author abstract) (21 Refs)

5. CORTICOLIPOTROPIN IMMUNOREACTIVITY IN SILENT CHROMOPHOBE ADENOMAS: A LIGHT AND ELECTRON MICROSCOPIC STUDY.

Hassoun J, Charpin C, Jaquet P, Lissitzky JC, Grisoli F, Toga M
Laboratoire d'Anatomie Pathologique et de Neuropathologie, 27, Bd Jean Moulin, 13885 Marseille Cedex V, France
Arch Pathol Lab Med; 106(1):25-30 1982

Twenty silent human pituitary adenomas were morphologically studied. Immunoperoxidase methods showed numerous adrenocorticotropic hormone-immunoreactive tumor cells in 14 cases by light microscopy and in one additional case by electron microscopy. Three of these cases were positive for beta-endorphin and one for beta-lipotropin by electron microscopy. These immunoreactions were found in undifferentiated tumors as well as in oncocytic adenomas, and could not be related to the presence of basophils by light microscopy. The peptides so detected in silent adenomas may have no biological activity and may correspond to common precursor molecule subunits. (Author abstract) (35 Refs)

6. PARATHYRIN (PARATHYROID HORMONE): RADIOIMMUNOASSAYS FOR INTACT AND CARBOXYL-TERMINAL MOIETIES.

Di Bella FP, Hawker CD
Lab. Procedures, Inc., Upjohn Co., Kalamazoo, MI
Clin Chem; 28(1):226-235 1982

Radioimmunoassay (RIA) procedures for measurement of intact or carboxy (C)-terminal parathyrin (parathyroid hormone; PTH) in blood are described in detail. Clinical applications of the assays are discussed. Both RIAs use the same bovine PTH for standards and radioiodination, the same dextran-coated charcoal preparation (for separation of antibody-bound and free 125I-labeled PTH), and the same types of equipment. The major difference between the assays is that the antiserum against intact PTH was produced in a guinea pig immunized with bovine PTH conjugated to bovine serum albumin; the antiserum against C-terminal PTH was produced in a guinea pig immunized with a human C-terminal PTH fragment. The two PTH assays have achieved a consistent record of performance, reliability, and clinical usefulness. Applications of the assays include the diagnostic evaluation of patients with hypercalcemia, hypocalcemia, or chronic renal failure and preoperative venous catheterization to localize hyperfunctioning parathyroid tissue. Causes of hypercalcemia identified by PTH measurements include parathyroid adenomas, ectopic PTH secretion by nonthyroid cancers, and malignant tumors that do not produce immunoreactive PTH. (35 Refs)

7. BIOLOGICAL AND BIOCHEMICAL PROPERTIES OF HUMAN CHORIONIC GONADOTROPIN FROM URINE OF PATIENTS WITH HYDATIDIFORM MOLE AND ITS RADIOIMMUNOASSAY.

Nishimura R, Hamamoto T, Tanabe K, Takemori M, Ashitaka Y, Tojo S
Dept. Obstetrics and Gynecology, Kobe Univ. Sch. Medicine, Kobe, Japan
Nippon Naibunpi Gakkai Zasshi; 57(11):1632-1644 1981

Human chorionic gonadotropin (hCG) was extracted from the urine of four women (21, 24, 24, and 26 yr old, respectively) prior to removal of hydatidiform moles. The hCG was extracted and purified from the urine samples, and various biological and biochemical tests were performed with the hydatidiform hCG. The tests included diethylaminoethanol-cellulose ion-exchange chromatography, sephadex G-100 gel-chromatography, sodium dodecyl sulfate disc electrophoresis, amino acid analysis, immunological activity of the hCG, biological activity of the hCG with respect to young rat ovaries, receptor assays, and in vivo Parlow rat ovaries, and radioimmunoassay (RIA; antiserum or 125I labeling). Immunological and biological activities of the urinary hCG from the four patients was equivalent to those observed for urinary hCG from normal pregnant women. Amino acid analysis indicated that the hydatidiform mole hCG and normal pregnancy hCG were very similar and the hydatidiform mole hCG was constructed of alpha and beta subunits. An RIA system for hydatidiform mole urinary hCG was established, and this method correlated well with the usual methods used to determine concentrations of serum hCG in normal pregnant women and in patients with trophoblastic diseases. (19 Refs) (In JPN)

8. COMMERCIAL RADIOIMMUNOASSAY FOR BETA SUBUNIT OF HUMAN CHORIONIC GONADOTROPIN: FALSELY POSITIVE DETERMINATIONS DUE TO ELEVATED SERUM LUTEINIZING HORMONE.

Fowler JE, Platoff GE, Kubrock CA, Stutzman RE
Univ. Virginia Sch. Medicine, Charlottesville, VA, 22908
Cancer; 49(1):136-139 1982

Among 17 men who had received seemingly curative treatment for unilateral non-seminomatous germ cell tumors for the testis and who had consistently normal serum human chorionic gonadotropin (HCG) levels at a reference laboratory, 7 (41%) had at least one falsely positive commercial serum HCG determination. To investigate the cause of these falsely positive determinations the authors measured the cross reactivity of luteinizing hormone (LH) and follicle stimulating hormone (FSH) standards in the commercial HCG assay, and studied the relationships between commercial HCG levels and serum LH levels, serum FSH levels and gonadal status in men with and without normal gonadal function. The falsely positive HCG determinations appeared to be due to elevated serum LH levels and cross reactivity of LH in the commercial HCG assay because: (1) there was substantial cross reactivity of the LH standards in the commercial assay, (2) the serum LH was elevated in four of six men with solitary testes, (3) there was a striking correlation between elevated serum LH levels and falsely elevated commercial HCG levels in 10 men with solitary or absent testes, and (4) there were no falsely positive HCG determinations in 13 normal men but there were falsely positive HCG determinations in 7 of 10 anorchid men. (Author abstract) (8 Refs)

9. CHORIONIC GONADOTROPIN SYNTHESIS AND GENE ASSIGNMENT IN HUMAN:MOUSE HYBRID CELLS.

Kohler PO, Riser M, Hardin J, Boothby M, Boime I, Norris J, Siciliano MJ
Dept. Medicine, Univ. Arkansas, Little Rock, AR
Adv Exp Med Biol; 138:405-418 1982

Chorionic gonadotropin (hCG) was studied using somatic cells as a technique for mapping the structural genes for hCG and human:mouse hybrid cells. Analysis of hybrid clones producing hCG and correlation with the retention of certain human chromosomes permitted localization of the hCG genes. Enzymatic chromosome markers in hybrid clones, percentages of cells retaining each human chromosome by morpho logy, and relationship of hCG synthesis to chromosomes 10 and 18 in subclones of 124c-1 are presented. (32 Refs)

CLINICAL, DIAGNOSTIC AND PROGNOSTIC STUDIES

10. BROMOCRIPTINE REDUCES PITUITARY TUMOR SIZE AND HYPERSECRETION: REQUIEM FOR PITUITARY SURGERY?

Spark RF, Baker R, Bienfang DC, Bergland R
Steroid Res. Lab., Beth Israel Hosp., 330 Brookline Ave, Boston, MA, 02215
JAMA; 247(3):311-316 1982

Twelve patients with pituitary tumor whose prior treatment included surgery and radiotherapy in four, surgery alone in four, radiotherapy alone in one, and none in three were studied. Nine had hyperprolactinemia, two had elevated serum growth hormones, and one had no pituitary hormone excess. Visual field defects were present in six. All had pituitary-gonadal insufficiency manifested as impotence or amenorrhea. All were treated with bromocriptine, 7.5 to 25 mg daily, and followed up for 8 to 27 (x 15) months. Serum prolactin levels decreased to normal in seven of nine patients. Serum growth hormone values were normalized in both acromegalics. When hormone levels were reduced to normal, pituitary tumor size decreased. Vision was restored to normal in five of six patients, including one patient with pituitary tumor but no pituitary hormone excess. Bromocriptine corrects the physiological defects associated with pituitary tumors that have been incompletely treated with surgery, radiotherapy, or both and may be a useful primary treatment for patients with pituitary tumors. (Author abstract) (35 Refs)

11. TREATMENT OF HYPERPROLACTINEMIC STATES WITH DIFFERENT DRUGS: A STUDY WITH BROMOCRIPTINE, METERGOLINE, AND LISURIDE.

Crosignani PG, Ferrari C, Liuzzi A, Benco R, Mattei A, Rampini P, Dellabonzana D, Scarduelli C, Spelta B
Fourth Dept. Obstetrics and Gynecology, Univ. Milan, Via Melloni 52, Milan, Italy
Fertil Steril; 37(1):61-67 1982

One hundred ninety-one hyperprolactinemic patients (178 women and 13 men; 54 with pituitary macroadenoma, 53 with microadenoma, and 84 with idiopathic disease) were treated for 2 to 48 mo with one or two of the following prolactin (PRL)-lowering drugs: bromocriptine, metergoline, and lisuride. All of the three drugs used were highly effective in lowering PRL levels and restoring gonadal function both in females and in males in the majority of patients with either idiopathic or tumorous disease. In poorly responsive patients, increasing the drug doses resulted in further PRL lowering for all the three drugs. Mild side effects were frequently encountered with initiation of drug treatment but spontaneously subsided in most cases; severe side effects, necessitating stopping of the treatment, occurred in only 12 instances, but changing of the drug allowed PRL-lowering treatment to be continued in 11 of them. (Author abstract) (21 Refs)

12. HYPERPROLACTINEMIA - THE UNDERLYING PHYSIOLOGY.

Maxson WS, Hammond CB
Vanderbilt Univ. Medical Center, Nashville, TN
Contemp Obstet Gynecol; 19(1):49-52,55-56,59,63 1982

The causes of hyperprolactinemia in neoplastic and non-neoplastic diseases are discussed. Prolactin levels fluctuate normally throughout a woman's life; prolactin is released episodically in pulses with a diurnal variation. The only certain functions of prolactin in humans are inducing development of the lobuloalveolar system of the breasts and initiating lactogenesis and milk secretion. High levels of estrogen and possibly prolactin inhibit lactation at the level of the breast. A variety of drugs may stimulate prolactin synthesis and secretion. Neoplastic causes of hyperprolactinemia include (1) inhibition of prolactin inhibiting factor (PIF) by hypothalamic tumors or pineal tumors (either primary or metastatic), (2) interruption of PIF transport due to pituitary stalk compression subsequent to hypothalamic or pituitary tumors, and (3) prolactin-secreting tumors, ie acromegaly, Cushing's disease, Nelson's disease, or microadenoma or macroadenoma of the pituitary, and ectopic tumor production from breast or bronchogenic carcinoma or hypernephroma. (31 Refs)

13. WHEN AND HOW TO TREAT PATIENTS WITH PROLACTIN DISORDERS.

Maxson WS, Hammond CB
Vanderbilt Univ. Medical Center, Nashville, TN
Contemp Obstet Gynecol; 19(1):67-68,73-76,81-82,88 1982

The treatment of patients with hyperprolactinemia is discussed. Approx 50-95% of patients with pituitary tumors have elevated prolactin levels. About 36% with amenorrhea and hyperprolactinema have pituitary tumors. Patients with microadenomas usually are symptomless. Degree of prolactin elevation correlates with the likelihood of pituitary tumor. Prolactinomas usually are evidenced by prolactin levels greater than 50 nanograms (ng)/ml. About 10% of patients with prolactin levels less than 100 ng/ml and 25-75% of those with prolactin levels above greater than 100 ng/ml will have pituitary adenomas. Essentially all patients whose levels exceed 300 ng/ml have pituitary tumors. Prolactinomas are detectable on skull x-rays in only 30% of patients. Currently no way exists to predict the biologic behavior of a pituitary prolactinoma. Four basic therapeutic approaches to treating prolactinomas include radiotherapy, surgery, drugs, and observation. Radiotherapy consists of 4,500-5,000 rads to the tumor over 4-5 wk. Bromocriptine is the agent of choice for hyperprolactinemia in women who are infertile and have no demonstrable pituitary tumor. Surgery or radiotherapy is indicated for women with a definite microadenoma or macroadenoma. (26 Refs)

14. PROLACTINOMAS, TESTOSTERONE-BINDING GLOBULIN, AND ANDROGEN METABOLISM.

Vermeulen A, Ando S, Verdonck L
Dept. Endocrinology-Hematology, Academic Hosp., Univ. Ghent, B-9000 Ghent, Belgium
J Clin Endocrinol Metab; 54(2):409-412 1982

To study the mechanism by which PRL might influence the metabolism of androgens, the testosterone-binding capacity of testosterone-estradiol-binding globulin (TeBG) as well as the free testosterone (T) fraction were determined in patients with prolactinoma. In untreated patients with prolactinoma, the TeBG capacity was decreased and the free T fraction was increased. Whereas in males, the plasma (free) T concentration was decreased, the apparent free T concentration was increased in women. The increased free T fraction had as a consequence an increase in MCRs of both T and 5alpha-androstan-17beta-ol-3-one; the MCR of androstenedione was normal. It is concluded that besides the well known factors, such as estrogens, androgens, and thyroid hormones, PRL appears, at least in prolactinoma patients, to influence the TeBG level. (Author abstract) (26 Refs)

15. THE EFFECTS OF HODGKIN'S DISEASE AND COMBINATION CHEMOTHERAPY ON GONADAL FUNCTION IN THE ADULT MALE.

Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Beardwell CG
(c/o Shalet) Dept. Endocrinology, Christie Hosp., Wilmslow Road, Manchester M20 0BX, England
Cancer; 49(3):418-422 1982

The effects of Hodgkin's disease and quadruple chemotherapy on gonadal function have been investigated in 93 male patients with Hodgkin's disease. Nineteen men were studied before they received chemotherapy. Fifteen of the 19 had a sperm count of 20 million/ml or greater and motility was at least 40% in all 15. In the remaining 74 men, gonadal function was studied after completion of chemotherapy (6 mo-8 yr). Semen was obtained from 49 men who had received six or more courses of MVPP. Forty-two were azoospermic and 5 of the remaining 7 had a sperm count below 1 million/ml. Decreased libido and sexual activity was common during treatment but in the majority of men these returned to normal after completion of chemotherapy. The median ***FSH and LH levels*** and the median increments in semen FSH and LH levels after LHRH administration were significantly elevated compared with an age-matched control group. The mean testosterone level of the patients was significantly lower than in controls suggesting Leydig cell damage but androgen replacement therapy was not indicated in any individual patient. No evidence of hyperprolactinemia as a result of MVPP therapy was found.

These results suggest that sperm storage before chemotherapy represents the main possibility for these patients to have children after completing chemotherapy. Before starting chemotherapy, advice should be given to these patients concerning possible changes in sexual behavior during treatment and the very high incidence of permanent infertility following treatment. (Author abstract) (21 Refs)

16. SUBNORMAL 24-HOUR MEAN CONCENTRATION AND ABNORMAL 24-HOUR PROFILE OF PLASMA LH IN THE LUTEAL PHASE IN WOMEN WITH BREAST CANCER.

Zumoff B, Levin J, Kream J, Strain GW, Markham M, Fukushima DK

Clinical Res. Center, Montefiore Hosp. and Medical Center, Bronx, NY, 10467

Anticancer Res; 1(5):305-308 1981

Twenty-four-hr mean plasma luteinizing hormone (LH) levels were measured in 14 otherwise healthy women (31-52 yr old) with breast cancer (BC) and in 13 healthy regularly cycling women (22-51 yr old). Seven of the patients (6 with localized and 1 with metastatic disease) and nine of the controls were in the follicular phase (FP); seven of the patients (5 with localized and 2 with metastatic disease) and four of the controls were in the luteal phase (LP). Follicular LH levels in the control women ranged from 10-23 milli (m)IU/ml. Five of the seven patients studied during FP had LH levels within the normal range, but the other two had markedly subnormal levels (4.4 and 7.4 standard deviations below the normal mean). LP levels in controls were 11-26 mIU/ml. One of the LP cancer patients had 11 mIU/ml; the other six had levels that were below normal (3.6-9.6 mIU/ml). The difference from the normal mean was significant. The 24-hr plasma LH profiles of five BC patients in LP were clearly abnormal: both frequency and amplitude of the episodic secretory pulses were markedly subnormal. Subnormal mean LH levels and abnormal plasma LH profiles may represent a human counterpart of the slow-gonadotropin-releasing hormone-pulsing model described in primates, indicating a type of hypothalamic dysfunction that might antedate the development of BC or might be a consequence of the disease. (22 Refs)

17. ADRENOCORTICOTROPIC HORMONE, BETA-LIPOTROPIN, AND ENDORPHIN-RELATED PEPTIDES IN HEALTH AND DISEASE.

Loh YP, Loriaux LL

Lab. Developmental Neurobiology, Natl. Inst. Child Health and Human Development, NIH, Building 36, Room 2A21, Bethesda, MD, 20205

JAMA; 247(7):1033-1034 1982

Biosynthesis and processing of adrenocorticotropic hormone (ACTH), beta-lipotropin (b-LPH), and beta-endorphin in the anterior and intermediate lobes of the pituitary gland are reviewed with special emphasis on the role of opiate-like peptides in differential diagnosis of Cushing's syndrome (CS). Since incomplete processing of pro-opiocortin molecule is characteristic for oat cell carcinoma of the lung, thymoma, pancreatic adenocarcinoma, and medullary carcinoma of the thyroid, detection of intact ACTH in the blood plasma of CS patients can indicate the presence of nonpituitary neoplasms. (18 Refs)

18. CUSHING'S DISEASE: TRANSIENT SECONDARY ADRENAL INSUFFICIENCY AFTER SELECTIVE REMOVAL OF PITUITARY MICROADENOMAS; EVIDENCE FOR A PITUITARY ORIGIN.

Fitzgerald PA, Aron DC, Findling JW, Brooks RM, Wilson CB, Forsham PH, Tyrrell J B

Metabolic Res. Unit, Univ. California,, 1143 HSW, San Francisco, CA, 94143

J Clin Endocrinol Metab; 54(2):413-422 1982

Of 12 patients with Cushing's disease who had successful selective microadenoma resection documented by clinical remission and reversal of hypercortisolism, 11 developed postoperative hypoadrenalism with deficient adrenal responsiveness to exogenous ACTH. The ACTH and glucocorticoid deficiency was not caused by the surgical procedure or hydrocortisone replacement, since it resolved despite replacement therapy; further, adrenal insufficiency did not occur in 10 acromegalic patients who received the same operation and identical glucocorticoid therapy. Other pituitary functions were not impaired postoperatively. We conclude that (1) the hypercortisolism caused by an ACTH-secreting pituitary microadenoma suppresses the normal pituitary secretion of ACTH and often that of GH and LH; (2) this suppression persists postoperatively, but gradually resolves in most patients; (3) a normal cortisol response to ACTH is a good indication that the pituitary-adrenal axis has recovered; (4) there is no evidence of a persisting hypothalamic defect after removal of ACTH-secreting microadenomas; and (5) pituitary microadenomas appear to be the primary cause of Cushing's disease in these patients. (65 Refs)

19. INFREQUENT ELEVATION OF PLASMA ACTH IN PATIENTS WITH BRONCHOGENIC CARCINOMA.

Davis S, May PB
Veterans Admin. Medical Center, East Orange, NJ, 07019
Am J Med Sci; 283(1):2-7 1982

Older methods for radioimmunoassay of ACTH in human plasma have detected a high frequency of plasma ACTH elevation in patients with lung cancer, even in the absence of Cushing's syndrome. It now appears evident that these assay systems measure biologically inactive forms and fragments of ACTH. Since ectopic Cushing's syndrome may be clinically atypical, a radioimmunoassay for ACTH that correlates with the clinical state would be of value. Accordingly, circulating plasma corticotropin (ACTH) levels were measured in 39 consecutive patients with biopsy-proven, untreated lung cancer, all without evidence of Cushing's syndrome. In only one instance was ACTH found to be elevated by the method of assay used. Two interpretations are justified: (1) elevated plasma ACTH levels are infrequent in patients with lung cancer, or (2) ACTH measurements vary according to the assay system used. (Author abstract) (7 Refs)

20. CLINICAL IMPLICATIONS OF ECTOPIC HORMONE PRODUCTION IN SMALL CELL CARCINOMA OF THE LUNG.

Hansen M
Dept. Internal Medicine C, Bispebjerg Hosp., 2400 Copenhagen NV, Denmark
Dan Med Bull; 28(6):221-236 1981

The production in small cell carcinoma (SCC) tumors of the lung of hormonal polypeptides related to the APUD system is reviewed with special reference to clinical implications. At the diagn osis of SCC, plasma levels of ACTH, plasma or urinary antidiuretic hormone (ADH), and/or serum calcitonin (CAL) are elevated in many patients. While measurement of these hormones is not helpful in identifying lung cancer, there determination help identify the tumor as SCC. Measurements of the cerebrospinal fluid:blood ratios of ACTH and ADH and comparisons with computed tomographic scans may be helpful in the evaluation of SCC patients with and without CNS metastases. The concentrations of these markers, if present, vary independently of each other. The pretreatment peripheral concentrations of these markers, the presence or absence of elevated marker titers, and the presence or absence of clinical syndromes related to the ectopic hormones, are unrelated to response rate and long-term results. Consequently, these markers cannot be reliably used for tumor staging, prognosis of evaluating response to therapy. Elevated pretreatment levels of CAL tend to recur when the SCC recurs, but this is not necessarily the case in most patients with elevated ACTH and/or ADH levels. Further research may identify some marker substances(s) having greater specificity for bronchial APUD cells and therefore the bronchial apudomas (SCC). (170 Refs)

21. BLOOD LEVELS OF BETA-ENDORPHIN AND BETA-LIPOTROPIN IN CUSHING'S DISEASE.

Slavnov VN, Valueva GV, Luchitskii EV, Iakovev AA
Lab. Radiology, Res. Inst. Endocrinology and Metabolism, Kiev, USSR
Ter Arkh; 53(12):107-110 1981

Blood levels of the neuropeptides beta-endorphin and beta-lipotropin were studied in 28 patients (17-52 yr old) with Cushing's disease (CD) and were compared with blood levels of corticotropin. The active stage of the CD was characterized by a significant increase in concentration of the neuropeptides. Normal blood levels of corticotropin were detected in 55% of the patients with active CD. Remission of the CD was characterized by normalization of the levels of the beta-endorphin and the beta-lipotropin. (12 Refs) (In RUS)

22. URINARY MELATONIN LEVELS IN HUMAN BREAST CANCER PATIENTS.

Bartsch C, Bartsch H, Jain AK, Laumas KR, Wetterberg L
Fichtenweg 6/110, D-7400 Tubingen 1, W. Germany
J Neural Transm; 52(4):281-294 1981

Urinary melatonin levels (UML) were measured to investigate the link between the pineal gland and breast cancer from the therapeutic and analytical angle. Studies were conducted with melatonin since it is the best documented hormone of the pineal gland. UML were measured in postmenopausal women in advanced stages of breast cancer and compared with controls. Melatonin excretion patterns of cancer patients were not synchronized as compared to patterns of controls. Results suggest that pineal melatonin secretion may be modified quantitatively and rhythmically in breast cancer patients. (40 Refs)

23. 'THYREOTROPIC HORMONE RELEASING-HORMONE' (TRH) LOADING TESTS IN EUTHYROID PATIENTS WITH AUTONOMOUS ADENOMA.

Foldes J, Banos Cs, Krasznai I
I. Belgyogyaszati Klinika, Semmelweis Orvostudomanyi Egyetem, Budapest, Hungary
Orv Hetil; 123(1):27-30 1982

TRH loading tests were performed in 46 euthyroid patients with autonomous thyroid adenomas. The thyroid-stimulating hormone (TSH) response was normal in 18/46 patients (Group I), and reduced in 28/46 (Group II). The serum total thyroxin and triiodothyronines levels were normal in both subgroups, even though the levels were higher, but still within normal limits, in Group II than in Group I. The free thyroxin level was at the upper limit of the normal range in Group II, but the difference between the two groups was statistically significant. The serum reverse triiodothyronines levels were slightly higher in Group II than in Group I, while the thyroxin-binding globulin (TBG) level was lower in Group II than in Group I, even though the difference was not significant. The serum TSH increased significantly upon the TRH loading in Group I, but it remained unchanged in Group II. Normal prolactin reaction to TRH was seen in both groups. The increases in the serum free thyroxin level, in the thyroxin/TBG and triiodothyronines/TBG quotients, as well as the pathological TSH response to TRH loading in euthyroid patients with autonomous adenoma can be considered a pretoxic sign. The findings indicate that the prolactin-producing cells of the pituitary gland respond to changes in the serum thyroid hormone levels much less sensitively than do the TSH-producing cells. (21 Refs) (In HUN)

24. SUPPRESSIVE THERAPY FOR RADIATION-ASSOCIATED NODULAR THYROID DISEASE: DOUBLE-BLIND STUDY WITH T3 AND DESICCATED THYROID.

Tamura K, Shimaoka K, Tsukada Y, Razack MS, Sciasicia M
Dept. Medicine, Miyazaki Medical Coll., Kiyotake, Miyazaki 889-16, Japan
Jpn J Clin Oncol; 11(3):457-462 1981

Suppressive therapy with either triiodothyronine (T3, 50 mg/day) or desiccated thyroid (DT, 120 mg/day) was carried out in a double blind study in 250 patients over a period of 6 mo. The patients had received radiation therapy (estimated av 400 rads) for various conditions and were an av of 27 yr (11-52 yr) before thyroid abnormalities were detected in routine screening; many had exhibited pretreatment thyroid abnormalities of various kinds. Responses to therapy were as follows: complete response (T3, 37/124; DT, 35/126), partial response (T3 27/124; DT 34/126), improvement (T3, 17/124; DT, 16/126), and no change or progression (T3, 43/124; DT 41/126). Thyroid scan did not show differences that agreed with responses. Thyroidectomy was performed on 58 patients who had not shown nodule disappearance after 6 mo. Predominant pathologic diagnoses were, carcinoma (11), chronic thyroiditis (26), adenoma (6) , colloid nodule (7), and other (8). The results show the value of a screening program for high-risk patients. (22 Refs)

25. RADIOIODINE TOTAL BODY SCAN VERSUS SERUM THYROGLOBULIN LEVELS IN FOLLOW-UP OF PATIENTS WITH THYROID CANCER.

Colacchio TA, LoGerfo P, Colacchio DA, Feind C
Dept. Surgery, Coll. Physicians and Surgeons of Columbia Univ., New York, NY
Surgery; 91(1):42-45 1982

Two groups of patients were studied to compare the efficacy of serum thyroglobulin (Tg) levels to 131I total body scans in the follow-up of patients with thyroid cancer. All of the group of 30 patients without recurrence had undetectable Tg levels both on and off thyroid hormone replacement, and all had negative total body scan results although 8 patients, showed uptake in remnant thyroid tissue. In the second group of 37 patients with documented recurrent or metastasis disease, 34 (92%) had positive serum Tg levels, although the levels in 5 of these patients were undetectable while on thyroid replacement, and 31 (84%) had positive total body scan results. The false negative results of the two tests were not overlapping, and of those with positive Tg levels, 29 showed a significant increase once thyroid hormone therapy had been withdrawn. We conclude that although the percentages of positive Tg levels and body scan results in patients with recurrent disease are similar, both tests are required to minimize the number of patients with undiagnosed metastases. Second, thyroid-stimulating hormone suppression has a definite although unpredictable effect on serum Tg levels in patients with thyroid cancer, and thyroid hormone should be withdrawn prior to measurement of serum Tg to minimize the number of false negative results. (Author abstract) (13 Refs)

26. PLASMA LEVELS OF THYROXINE AND TRIIODOTHYRONINE IN WOMEN WITH BREAST CANCER.

Zumoff B, O'Connor J, Levin J, Markham M, Strain GW, Fukushima DK
Clinical Res. Center, Montefiore Hosp. and Medical Center, Bronx, NY, 10467
Anticancer Res; 1(5):287-291 1981

Plasma thyroxine (T4) and triiodothyronine (T3) levels were measured in women with breast cancer (BC). Two groups of BC patients were studied, one consisting of 29 women rigorously selected (21 with localized disease, 8 with metastatic disease) and the second of 43 consecutive unselected women with BC in all stages. Three control groups were studied, one consisting of 22 women with other than breast cancer, the second of 21 women with miscellaneous noncancerous illnesses, and the third of 27 healthy women. Twenty-four-hr plasma T3 and T4 levels in the normal women and in the selected BC patients showed no significant difference between the groups with respect to T3 concentration but a marked, significant difference between the groups with respect to T4 level. Cancer patient T4 levels were greater by 33%. The mean 8 a. m. 'spot' plasma T4 level in unselected BC patients was 8.8 ug/deciliter, a significant 21% elevation above the level in normal women. The values for women with other than breast cancer and with miscellaneous non-cancerous illnesses were essentially identical to the value of women with BC, ie significantly elevated above normal levels. BC patients as a group show significant hyperthyroxinemia; this finding may represent a second nonspecific abnormality of thyroid hormone disease after hypotriiodothyroninemia. (39 Refs)

27. IMMUNOREACTIVE CALCITONIN IN LEUKAEMIA (MEETING ABSTRACT).

Oscier DG, Hillyard CJ, Foa R, Incarbone E, Goldman JM, McIntyre I, Galton DA
Hammersmith Hospital, London, England
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

The concentration of immunoreactive human calcitonin (i-HTC) was measured in the plasma of 101 patients with chronic granulocyte leukemia (CGL) in chronic phase, 16 patients with CGL in myeloblastic transformation, and 29 patients with acute myeloid leukemia (AML) of presentation or in relapse. Raised levels of i-HCT were found in 96 at the chronic phase CGL patients and in all cases of CGL in myeloblastic transformation and of AML. The levels were significantly higher in the blastic phase than in the chronic phase of CGL. In contrast plasma i-HCT levels from patients with acute lymphoblastic leukemia, chronic lymphocytic leukemia and the majority of patients with AML in remission were low or undetectable. The possibility that the hormone may be derived from the leukemia cells themselves was suggested by the finding of i-HCT in th supernatant media of short term cultures of peripheral blood WBC from patients with CGL and AML, and from extracts of these cells. High pressure liquid chromatography performed on extracts of chronic phase CGL cells showed that the immunoreactive peak coincided with that of calcitonin monomer. We conclude that myeloid leukemia cells synthesize and release i-HCT, and measuring plasma levels may be of value in monitoring clinical progress in individual patients. (no Refs)

28. SERUM AND URINE CALCITONIN LEVELS IN PATIENTS WITH MEDULLARY THYROID CARCINOMA AND WITH NON-THYROIDAL CANCER AND THEIR IMMUNOLOGICAL SIZE-HETEROGENEITY.

Morimoto S, Onishi T, Imanaka S, Kumahara Y, Okada Y, Takai S, Miyauchi A, Nishioka Y
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Nippon Naibunpi Gakkai Zasshi; 57(8):1127-1138 1981

Levels of human calcitonin (hCT) were measured in serum and urine samples from 66 normal subjects (35 men, 31 women; 18-45 yr old), 24 patients with medullary thyroid carcinoma (MTC), and 277 patients with non-thyroid malignant tumors (NTMT). Serum samples were obtained from patients in the morning prior to eating and were centrifuged within 2 hr of sampling; levels of serum hCT were determined with the aid of radioimmunoassay (RIA). Levels of urinary hCT were measured with RIA after the urine samples were boiled for 2 min, mixed with blue dextran, and passed through a Bio Gel column. Levels of serum hCT were less than 25 to 140 picog (pg)/ml in 66/66 normal subjects, 0.24-215 nanog (ng)/ml in 24/24 patients with MTC, and less than 25 to 2,013 pg/ml in 277/277 patients with NTMT. Abnormally high (greater than 150 pg/ml) levels of serum hCT were observed in 44 NTMT patients (10/83 with gastric cancer, 4/25 with lung cancer, 1/25 with large intestine cancer, 18/43 with liver cancer, 2/21 with breast cancer, 1/2 with kidney cancer, and 8/64 with unknown types of cancer). Levels of urinary hCT were 66-270 pg/mg creatinine (CR) in 56/66 normal subjects, 1.7-520 ng/mg CR in 11/24 patients with MTC, and 60-83,000 pg/mg CR in 82/277 patients with NTMT. Levels of urinary hCT were 3.4-20.8x higher than levels of serum hCT in 11/24 patients with MTC. Four distinct forms of immunoreactive calcitonin (IC) were observed in serum samples from three patients with MTC, and one main form of IC was observed in a urine sample from a patient with oat cell carcinoma of the lung. Measurement of serum and urinary hCT levels was thought to be useful for detecting cases of MTC and ectopic calcitonin-secreting tumors. (29 Refs) (In JPN)

29. THE PROGNOSTIC AND BIOLOGICAL SIGNIFICANCE OF CELLULAR HETEROGENEITY IN MEDULLARY THYROID CARCINOMA: A STUDY OF CALCITONIN, L-DOPA DECARBOXYLASE, AND HISTAMINASE.

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J Clin Endocrinol Metab; 54(2):233-240 1982

We evaluated the cellular distribution of calcitonin (CT), L-dopa decarboxylase (DDC), and histaminase [diamine oxidase (DAO)] in 33 patients with medullary thyroid carcinoma (MTC). CT immunostaining was uniform (greater than 90% of the cells) and intense (4+) in lesions from seven patients with

C-cell hyperplasia and six with microscopic MTC: conversely, patchy CT staining (less than 40% of the cells) and diminished intensity (1+) were found in metastases from eight patients who died of virulent disease. In 17 patients who underwent thyroidectomy for macroscopic cervical MTC with no evident distant metastases, CT staining was intense (3-4+) and homogeneous (greater than 90%) in 11 subjects who were well 0.5-16 yr postoperatively. Six patients with similar clinical presentations had heterogeneous staining for CT in primary tumor (less than 40% of the cells; 1-2+ intensity); five died of disseminated MTC 0.5-5 yr postoperatively (p less than 0.001). Biochemical studies of distant metastases revealed an inverse relationship between the distribution of CT and that of both DDC (r =-0.71; p less than 0.01) and DAO (r =-0.81; p less than 0.001). We conclude that cellular heterogeneity in MTC tissue is associated with a distinct biochemical pattern, and its presence, whether in a primary or metastatic lesion, indicates a virulent neoplasm associated with a grave prognosis. (Author abstract) (34 Refs)

30. DISTINCTION BETWEEN PARANEOPLASTIC HYPERCALCEMIA (HCA) AND HYPERCALCEMIA OF PRIMARY HYPERPARATHYROIDISM (PHP) BY MEANS OF BIOCHEMICAL PARAMETERS (MEETING ABSTRACT).

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UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

HCa is the most frequent metabolic complication of malignant disease. Its major differential diagnosis is PHP. This often relies on biochemical parameters of parathyroid function, such as 1) plasma parathyroid hormone (PTH), 2) chloremia/phosphoremia ratio (Cl/P), 3) nephrogenous cyclic AMP (NcAMP). We studied the diagnostic reliability of these 3 parameters: in 57 patients with HCa, PTH was found to be suppressed in 12, low normal in 33, high normal in 10, and elevated in 2. Only in these 2 patients paraneoplastic secretion of PTH could be suspected. In 45 patients with PHP, PTH was low normal in 2, high normal in 12, and elevated in 31. The overlap between the 2 groups occurred in mild hypercalcemia only, but not with a plasma calcium of over 3 mmol/1. 2) The Cl/P was measured in 29 patients with HCa and 29 patients with PHP. Five patients with HCa and all patients with PHP had values above normal, but there was no overlap between the 2 groups, except of one single case with HCa. 3) The NcAMP was normal or low in all 10 patients with HCa studied, and above normal in 9 out of 10 patients with PHP, without overlap. Conclusion: with none of the 3 parameters suppressed PTH secretion could be documented in all patients with HCa. As routine analysis Cl/P is the most practical test for an almost complete distinction between the 2 causes of hypercalcemia. Complete separation was obtained by NcAMP, and by PTH when hypercalcemia exceeded 3 mmol/1. (no Refs)

31. A STUDY OF PROSTAGLANDIN E2, PARATHORMONE, AND RESPONSE TO INDOMETHACIN IN PATIENTS WITH HYPERCALCEMIA OF MALIGNANCY.

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Cancer; 49(3):556-561 1982

In order to evaluate the relationship of PGE2 to hypercalcemia in cancer patients, 101 patients were screened with a radioimmunoassay for plasma prostaglandin E2 (PGE2) (NL less than 100 pg/ ml). Of the 101 patients, 31 were hypercalcemic. Mean PGE2 (+- SEM) of the 31 patients was 199 +-36 pg/ ml. Among the 70 normocalcemic patients, mean +- SEM PGE2 was 85 +-12 pg/ml (range = less than 25-225 pg/ml) (p less than 0.001). Seventeen hypercalcemia patients were initially treated with saline and furosemide, then were prospectively screened for serum parathormone (iPTH) and PGE2. Fourteen of 17 patients were then treated empirically with indomethacin (25 mg bid) for 72 hours and the PGE2 assay was repeated. Prior to therapy with indomethacin (mean +- SEM), CA++ = 12.2 + 1.5 mg/dl (NL 8.4-10.6 mg/dl), PGE2 = 87.1 +-36.8 pg/ml, (range = less than 25-209 pg/ml), and iPTH = 406 +-266 pg/ml (NL less than 400 pg/ml) (range = less than 100-825 pg/ml). PGE2 was elevated before treatment in 6/14 patients (breast, colon, renal, lung, neck tumors, and myeloma). Following treatment with indomethacin, PGE2 and calcium fell to normal levels in three patients (breast, colon, renal carcinomas). These results suggest: (1) A bimodal distribution of PGEs exists in hypercalcemic cancer patients. (2) There was some evidence of lack of whole molecule iPTH suppression in these patients. (3) Multiple stimuli of calcium mobilization may play an important etiologic role in a few hypercalcemic cancer patients and may explain the failure of indomethacin to control serum Ca++ in some patients with elevated PGE2. (Author abstract) (44 Refs)

32. PROBING THE CAUSES OF HYPERCALCEMIA.

Brown EM, Parfitt AM, Rasmussen H, Recker RR
No affiliation given
Patient Care; 16(2):41-44,46,47,50-52,57-59 1982

Causes of hypercalcemia are reviewed. Hypercalcemia in patients requiring hospitalization is most likely to be caused by a neoplasm, whereas most hypercalcemia among asymptomatic outpatients is caused by primary hyperparathyroidism. Hypercalcemia should be diagnosed only when repeated assays show persistently elevated calcium levels. One mechanism for the production of hypercalcemia in cancer patients is the presence of skeletal metastases. The tumor cells probably do not cause breakdown of the bone by directly encroaching on the bone. The mechanism may resemble the humoral mechanisms whereby malignancies increase bone resorption indirectly. These humoral mechanisms include the production of osteoclast-activating factor (some cancer cells may contain receptors resembling those present on osteoclasts), production of prostaglandins of the E series (a mechanism believed to be uncommon), and production of substances resembling parathyroid hormone (PTH) in biologic action. The ectopic production of PTH by neoplasms is probably rare. Pheochromocytomas may also be associated with hypercalcemia as part of the familial multiple endocrine adenomatosis Type II syndrome (medullary carcinoma of the thyroid, pheochromocytoma, and hyperparathy roidism). The release of catecholamines by pheochromocytomas may also stimulate the release of PTH or directly stimulate bone resorption. (14 Refs)

33. WHEN YOU SUSPECT HYPERCALCEMIA.

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Patient Care; 16(2):14-18,25-27,30-32,37 1982

Evaluation and treatment of suspected hypercalcemia are discussed. Physical examination, history (especially drug history), and several laboratory tests can usually distinguish between hyperparathyroid hypercalcemia and other forms of hypercalcemia not mediated by parathyroid hormone (PTH). In humoral, malignancy-associated hypercalcemia, urinary cyclic AMP levels are elevated. A complete blood count and RBC sedimentation test may disclose multiple myeloma or another hematologic malignancy. In hypercalcemia not associated with excess PTH, bone scans and skeletal x-rays may disclose a bone malignancy. Even if the patient has a malignancy (eg, breast cancer with bone metastases), the associated hypercalcemia might be caused by primary hyperparathyroidism or another benign condition. Review of the patient's previous laboratory tests may disclose evidence of chronic hypercalcemia. The most important factor in treatment of hypercalcemia is treatment of the underlying disease. Therapy designed to increase renal calcium excretion and reduce bone resorption include a short course of mithramycin (15-25 ug/kg) and a combination of glucocorticoids and calcitonin. At least in treatment of malignancy-associated hypercalcemia, the glucocorticoid-calcitonin combination can maintain nearly normal levels of serum calcium for 4-5 days longer than calcitonin alone. (3 Refs)

34. COEXISTENT MULTIPLE MYELOMA AND PRIMARY HYPERPARATHYROIDISM.

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JAMA; 247(6):823-824 1982

A patient with multiple myeloma and hypercalcemia responded to cytotoxic chemotherapy. However, hypercalcemia persisted. Because of the absence of lytic bone lesions, the presence of a low serum phosphate level, and a family history of possible primary hyperparathyroidism, the patient was evaluated for this disorder. Serum parathyroid hormone and urinary cyclic adenosine monophosphate levels were elevated. Exploration of the neck disclosed two enlarged parathyroid glands (1,850 mg and 210 mg), which were excised. After surgery, the patient's serum calcium levels remained normal for one year. Progressive myeloma bone disease developed that eventually resulted in recurrent hypercalcemia and death. Autopsy revealed only evidence of myeloma. (Author abstract) (9 Refs)

35. SERUM GASTRIN LEVELS IN PATIENTS WITH ACROMEGALY.

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Horm Metab Res; 13(12):714-715 1981

Enochs and Johnson (1976) have found that hypophysectomy decreased serum and antral gastrin content in the rat. The replacement of growth hormone reversed this effect, returning the gastrin levels toward normal. On the other hand, Rehfeld (1978) demonstrated the immunoassayable gastrin in the mammalian hypophysis. The presence of gastrin or gastrin-like peptide in the anterior and intermediate lobe cells of the hypophysis were also shown by immunohistochemical method by Lotstra, Vanderhaegen and Gilles (1980). These findings have encouraged us to investigate patients with pituitary tumors. (Author abstract) (4 Refs)

36. PLASMA SECRETIN LEVELS IN TOTAL PANCREATECTOMY AND PANCREATICODUODENECTOMY.

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Jpn J Surg; 11(6):433-439 1981

Biliary secretion after major pancreatectomy (PE) was evaluated by measuring secretory responses of plasma secretin levels (PSL) to intrajejunal infusion of HCl in patients who underwent total PE and pancreaticoduodenectomy (PED). PSL was measured in 11 patients who underwent total PE and 8 patients with PED. Ten patients who underwent gastrectomy served as controls. All patients after total PE had been diagnosed as having ductal carcinoma of the pancreas. Patients after PED included two patients with carcinoma of the head of pancreas, four with carcinoma of the ampulla, and two with carcinoma of the terminal bile duct. No significant statistical differences were noted in the mean basal PSL in all groups of patients and controls, although PSL in patients with PE and PED were lower than in controls. Following initiation of 0.1 N HCl infusion, PSL increased significantly during the first 15 min and returned to basal PSL within 60 min in all groups. Mean peak PSL were 98.6 +-10.0 picog (pg)/ml in patients with total PE, 159.0 +-23.1 pg/ml in patients with PED, and 166.6 +-30.0 pg/ml in controls. Significant statistical differences were noted at min 10, 15, and 20 between patients with PE and patients with PED, but no significant differences were noted between patients with PED and controls. Among patients with total PE, those with Billroth II type anastomosis showed a significantly impaired response compared with patients with Billroth I type anastomosis. Results showed that biliary secretion is more impaired in patients with total PE than in patients with PED. Billroth I type anastomosis for reconstruction procedure of the alimentary tract appears more feasible. In the case of major PE, much attention should be given to biliary secretion to decrease the possibility of ulcer occurrence at the anastomosis and to improve the digestion-absorption of fat. (11 Refs)

37. INTRAOPERATIVE BIOCHEMICAL LOCALIZATION OF INSULINOMA BY QUICK RADIOIMMUNOASSAY.

Teichmann RK, Spelsberg F, Heberer G
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Am J Surg; 143(1):113-115 1982

In patients with organic hyperinsulinism, intraoperative determination of insulin concentrations in veins draining the pancreas might help localize the tumor. We have developed a radioimmunoassay measuring insulin within 30 minutes. At operation, blood samples are taken at various sites in the splenic, superior mesenteric and portal veins for insulin determinations. In all six patients, the highest insulin concentrations correlated with the site of the tumor. Also, small insulinomas less than 1 cm in diameter could be found. In one patient the tumor appeared to secrete mainly proinsulin. By this procedure we hope to avoid blind distal resection of the pancreas and possibly invasive preoperative diagnostic procedures. (Author abstract) (7 Refs)

38. DIAGNOSIS OF INSULINOMA. DETERMINATION OF INSULIN, C-PEPTIDE AND PROINSULIN IN THE BLOOD TO DIFFERENTIATE BETWEEN ENDOGENOUS AND EXOGENOUS HYPERINSULINISM.

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Tidsskr Nor Laegeforen; 101(34-36):1957-1960 1981

Distinction between endogenous and exogenous hyperinsulinism in connection with the diagnosis of insulinoma is described on the basis of the report of the cases of five patients with suspected insulinoma, in three of which insulinoma was confirmed histologically upon surgery. One patient had many normal insulin levels during the 72-hr fasting. The blood glucose levels were low, indicative of insulinoma. Transhepatic vein catheterization with measurement of the insulin levels failed to show high insulin levels in any of the pancreatic veins. Preoperatively elevated plasma proinsulin levels decreased after extirpation of insulinoma in another patient. The diagnosis of insulinoma was established in another patient on the basis of low C-peptide levels together with high total insulin level. Increased insulin levels without increased C-peptide level and with reduced blood glucose levels were found in another tumor-free patient under the effect of exogenous insulin supply. The blood glucose and insulin levels should be determined at short intervals during a 72-hr fasting in patients with suspected insulinoma. If high insulin levels are found and self-afflicted hyperinsulinism is suspected, C-peptide and proinsulin should also be determined additionally. Proinsulin measurements are of great value in the absence of insulin antibodies. (10 Refs) (In NOR)

39. HUMAN CHORIONIC GONADOTROPINS.

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Dept. Obstetrics and Gynecology, Shanghai First People's Hosp., Shanghai, People's Republic of China
Zhonghua Fuchanke Zazhi; 16(2):117-120 1981

Advances in research and clinical applications of human chorionic gonadotropins (HCG) are reviewed. The following topics are covered: (1) chemical structure of alpha- and beta-HCG, (2) biological activities, (3) immunologic properties, (4) analytical methods for determining HCG, especially radioimmunoassay, and their application in diagnosis and treatment of trophoblastic diseases and tumors, and (5) use of HCG (especially beta-HCG) as antigen in the preparation of contraceptive vaccines. (29 Refs) (In CHI)

40. ENDOCRINE INTERRELATIONSHIPS IN PATIENTS WITH MALIGNANT TESTICULAR TUMORS.

Lunglmayr G, Kuber W, Spona J
Urologische Universitatsklinik, Alser Strasse 4, A-1090 Wien, Austria
Wien Klin Wochenschr; 93(13):411-414 1981

In 40 patients (16-47 yr old) with malignant germinal testicular carcinoma spermatologic and endocrinologic analyses were conducted. The specific endocrine activity of tumor tissue was determined through the beta-HCG level in serum before therapy. Beta-HCG positive results were obtained in 21 patients, beta-HCG negative results in 19 patients. Follicle stimulation hormone production of pituitary gland was suppressed by increased estradiol production due to increased beta-HCG production. The elevated estrogen level in serum was also the cause of gynecomasty. Spermiograms were strongly affected in all cases. (17 Refs) (In GER)

41. GRANULOCYTE DEMARGINATION BY EPINEPHRINE IN EVALUATION OF HYPERSPLENIC STATES.

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Scand J Haematol; 27(4):225-230 1981

The usefulness of the epinephrine stimulation test in detecting granulocytic hypersplenism is evaluated. In eight hypersplenic patients, an increment of the granulocyte count of 170% over baseline values was found, compared to 38% (p less than 0.001) in normal subjects and 44% (p less than 0.002) in patients neutropenic from other causes. No overlap of individual test results was found among the hypersplenic and the control groups. Epinephrine test discriminates between neutropenia from hypersplenism and neutropenia from other causes. Furthermore, this test is found to be a valuable adjunct to the hydrocortisone stimulation test in kinetic evaluation of neutropenia from any cause. (Author abstract) (14 Refs)

EFFECTS ON NORMAL AND NEOPLASTIC CELLS AND TISSUES

42. THE PRIMARY TISSUE CULTURE OF HUMAN ADRENOCORTICAL CONN'S ADENOMATA. I. THE SYNERGISTIC STIMULATION OF ADENOMATOUS CELL GROWTH BY PURINE CYCLIC NUCLEOTIDES AND BY ACTH1-24 AND ANGIOTENSIN II.

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Pathol Res Pract; 173(1/2):66-81 1981

Primary cultures of dissociated parenchymal cells from Conn's adenomata causing primary hyperaldosteronism were successfully set up by a method previously used with normal adult human and rat adrenocortical tissue. In such cultures the adenomatous cells largely prevailed (making up 87% of the whole cell population), could survive for lengthy terms (at least up to 30 days), and were endowed with a spontaneous, discrete capability to proliferate. The de novo RNA- and DNA-synthetic and mitotic activities of Conn's cells were markedly stimulated in cultures exposed between day 16 and 21 to daily doses of exogenous cyclic AMP, either alone or in equimolar association with cyclic GMP. A significantly weaker, though still prominent enhancement of adenomatous cell growth was elicited also by daily administrations of an equimolar mixture of ACTH1-24 and angiotensin II. In contrast, little stimulation or inhibition of growth or no effect at all could be observed when cyclic GMP, ACTH1-24, and angiotensin II were respectively administered, each by itself. The present results support the working hypothesis that Conn's adenomatous cell growth is orderly controlled by several hormonal factors, including angiotensin and ACTH, the actions of which are mediated by both cyclic AMP and GMP. (Author abstract) (39 Refs)

43. EFFECT OF MELATONIN ON EXPERIMENTAL TUMORS UNDER DIFFERENT PHOTOPERIODS AND TIMES OF ADMINISTRATION.

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J Neural Transm; 52(4):269-279 1981

Effects of melatonin (Mel) on tumor growth, dependence on the photoperiod and the time of administration, were examined. Swiss random-bred 8-10 wk old albino mice (25-35 g body wt) were used for the experiments. Mel solutions were freshly prepared prior to each experiment in concentrations of 1 mg/ml. Fibrosarcoma ascites (FSA) cells injected ip and Ehrlich ascites (ES) cells injected sc were used in the experiments. Performed experiments are presented. Under long photoperiods Mel shows opposite effects on FSA and ES tumors depending on the time of the day at which the compound was administered. Experiments under light:dark (L:D) = 13:11 with FSA bearing mice treated with Mel in the morning showed a 37% decrease in survival time as compared to the controls. Increase of 37% in survival time was observed in animals which received Mel in the late afternoon. The difference is significant. Mice with ES treated with Mel in the morning showed slight increase in tumor size (+12%). Mel injections in late afternoon had no effect, while Mel injections in the evening led to decrease in tumor size (-28%). The difference in av tumor size between animals receiving Mel in the late afternoon and controls is significant Experiments under L:D = 12:12 and L:D = 8:16 do not show such pronounced antagonistic effects. Results support the hypothesis that the effect of Mel on tumor growth is dependent on the photoperiod and the time of day of administration. Possible mechanisms involved in these effect are discussed. (28 Refs)

44. MODULATION OF IN-VIVO METABOLIC EFFECTS OF GAMMA-IRRADIATION BY THYROID STATUS MANIPULATIONS.

Wilhelm J, Sonka J
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Strahlentherapie; 157(11):762-765 1981

Animals made hypothyroid by propylthiouracil, gamma-irradiated and subsequently treated with triiodothyronine were compared with animals irradiated only. The influence of devised manipulations on energy metabolism was studied in rat liver mitochondria. The post-irradiation decrease of succinate-oxidase and cytochrome-oxidase activities was not observed in irradiated hypothyroid-triiodothyronine treated animals. The concentration of lipofuscin-like pigments, an indicator of radiation damage, was lowered. Possible explanations of these results are discussed. (Author abstract) (18 Refs)

45. EFFECT OF TREATMENT WITH GLUTAURINE ON HUMAN ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY (ADCC).

Lang I, Feuer L, Nekam K, Torok K, Kalmar L, Gergely P
Second Dept. Medicine, Semmelweis Univ. Medical Sch., H-1088 Budapest, Hungary
Immunol Commun; 10(6):499-509 1981

The effects of in vitro and in vivo treatment with glutaurine, a newly discovered parathyroid hormone possessing immunostimulative activity, on human antibody-dependent cell-mediated cytotoxicity (ADCC) were studied in 15 tumor patients and healthy subjects in a xenogeneic test system using chicken erythrocytes as target cells. A marked increase in 'K' cell activity was observed in eight tumor patients with originally low cytotoxic capacity, while originally normal ADCC activity of other tumor patients and healthy subjects was not significantly influenced by glutaurine treatment. The changes in cytotoxicity were not accompanied by changes in lymphocyte populations. Incubation of effector cells with glutaurine in vitro caused no change in ADCC activity in lymphocyte populations. Some similarities between the effects of glutaurine treatment on ADCC and that of dialyzable leukocyte extracts are discussed. (Author abstract) (33 Refs)

46. TROPHIC EFFECTS OF GASTRIN ON COLORECTAL NEOPLASMS IN THE RAT.

McGregor DB, Jones RD, Karlin DA, Romsdahl MM
Dept. Surgery, Univ. Nevada - Reno, 1000 Locust St., Reno, NV, 89520
Ann Surg; 195(2):219-223 1982

This study was designed to determine the effect of gastrin on colorectal neoplasms in the rat. Multiple colon and rectal cancers were induced in each of 57 rats with methylazoxymethanol. Animals were randomly assigned to groups: (1) antral exclusion, (2) antrectomy, (3) sham, or (4) sham with subsequent pentagastrin injections. Resulting tumors were analyzed for concentration and synthesis of DNA, RNA, and protein. The number of tumors per rat and distribution of tumors within the colons did not vary among groups. Antrectomy did not alter the gastrin level, and tumors developing in these animals did not differ from those of sham controls. Antral exclusion markedly raised serum gastrin levels. Both chronic endogenous hypergastrinemia and administration of exogenous pentagastrin significantly increased tumor synthesis and concentration of DNA, RNA, and protein. We conclude that gastrin exerts a trophic effect on colorectal neoplasms in rats. This biological phenomenon suggests a tumor regulatory role for the hormone. (Author abstract) (11 Refs)

47. ACTION OF INSULIN ON GLYCOGEN METABOLISM IN CULTURED HEPATOMA CELLS.

Staedel-Flaig C, Capeau J, Picard J, Beck JP
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Mol Cell Endocrinol; 24(3):283-291 1981

Characteristics of insulin action in ZHC cells, a hepatoma cell line characterized by its capacity to synthesize and store glycogen, were studied in order to compare it with the action of the hormone on normal adult or embryonic hepatocytes in vivo or in primary culture systems, and to approach control mechanisms of glycogenic function at a molecular level. Insulin, in a final concentration of 10(-8) M, was added at various times to the cultures and glycogen content was measured by (U-14C) glucose incorporation. Sensitivity of cells to insulin was correlated with culture development and was maximal in confluent monolayer cultures. After 2-3 hr of incubation with insulin, glycogen content was stimulated by net synthesis of new glycogen molecules and without affecting breakdown. Insulin action on the incorporation of tritiated leucine or thymidine into proteins or DNA was tested over a 24-hr period. Results indicated insulin acts directly on glycogen metabolism, and did not modify total cell protein or DNA synthesis. The ZHC cell line retains responsivness to insulin, and can provide a new model for the study of insulin regulation of glycogen metabolism in the absence of other hormones that modulate the same pathway. (21 Refs)

48. HEXOSE TRANSPORT IN UNDIFFERENTIATED AND DIFFERENTIATED BALB/C 3T3 PREADIPOSE CELLS: EFFECTS OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE AND INSULIN.

O'Brien TG
Wistar Inst. Anatomy and Biology, Philadelphia, PA, 19104
J Cell Physiol; 110(1):63-71 1982

The hexose transport system of BALB/c 3T3 (clone A31T) cells, both before and after adipose conversion, was characterized and its modulation by 12-O-tetradecanoylphorbol-13-acetate (TPA) and insulin was studied by 14C-2-deoxyglucose (2DG) uptake and 3-O-3H-methylglucose (3MG) transport assay. TPA stimulated both 2DG uptake and 3MG transport systems in the undifferentiated cells, with the concentration stimulating half-maximal response being 3 nano (n) M for the 2DG system and 30 nM for the 3M G system. TPA also stimulated both systems in differentiated cells, but 3MG transport decayed much more rapidly than the level of 2DG upatke. Stimulation of 2DG uptake in undifferentiated cells by protein factors and TPA was as follows: TPA greater than or equal to fetal bovine serum greater than or equal to epidermal growth factor; insulin (170 nM) had no effect. Insulin did not stimulate 3MG transport in undifferentiated cells, but did activate it in differentiated cells over the range 1.7 nM -1.7 uM, with half-maximal response occurring at 0.17 uM; TPA was stimulatory in both types of cells, with half-maximal response at 30 nM in both. When the agents were used together insulin caused a significant additional stimulation of 3MG transport system of that caused by TPA alone. Cycloheximide treatment of differentiated cells concurrently with, or 6 hr prior to, insulin had no effect on its stimulation of 3MG transport, but did cause a 75% inhibition of the TPA-stimulated response. Long-term exposure of differentiated cells to insulin abolished the 3MG-transport acute stimulation response to insulin, but not the TPA acute response; long-term exposure to TPA did not adversely affect either TPA or insulin response in differentiated cells. Apparently TPA and insulin stimulate hexose transport in adipose cells by different mechanisms. (30 Refs)

49. THE EFFECT OF BETA BLOCKADE ON THE REACTION OF PRESSURE AND MESENTERIC FLOW TO BIOGENIC AMINES IN NORMAL AND X-IRRADIATED RATS.

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Strahlentherapie; 157(3):208-212 1981

A beta-blocker, propranolol, was infused to control and irradiated rats the 1st and 3rd day after 2-kR x-ray irradiation. Blood pressure and mesenteric blood flow were recorded during infusion of biogenic amines (noradrenaline, dopamine, serotonin, acetylcholine and histamine). After beta-blockade, there was intensified increase in pressure and decrease in flow with increased overshoot after infusion of noradrenaline, no effect of the increase in pressure and flow after dopamine, but an enhanced increase in pressure and decrease in flow after serotonin. No effect on the decrease in pressure and flow was seen after acetylcholine, and a greater decrease in pressure and flow, after histamine. Irradiation altered the vascular reactivity, mainly for noradrenaline, serotonin and histamine. (Author abstract) (9 Refs)

EFFECTS OF ENDOGENOUS AND EXOGENOUS AGENTS ON NON-STEROID HORMONE ACTIVITY

50. DEFECTIVE CENTRAL NERVOUS SYSTEM DOPAMINERGIC FUNCTION IN RATS WITH ESTROGEN-INDUCED PITUITARY TUMORS, AS ASSESSED BY PLASMA PROLACTIN CONCENTRATIONS.

Casanueva F, Cocchi D, Locatelli V, Flauto C, Zambotti F, Bestetti G, Rossi GL, Muller E
(c/o Muller) Dept. Pharmacology, Univ. Milan, Via Vanvitelli, 32, 20129 Milan, I taly
Endocrinology; 110(2):590-599 1982

Mature cycling female rats were each injected at 3-wk intervals with 2 mg estradiol valerate (EV) in sesame oil. Controls received an equivalent volume of sesame oil. The administration of EV induced, at first, hyperplasia and then, 10 wk after the first EV injection, adenomatous changes in the pituitary gland. Concurrently, there was a striking rise in plasma PRL concentrations, which reached values of about 2 ug/ml at 25 wk. Acute administration of nomifensine (NOM), an indirectly acting dopamine (DA) agonist, to EV-injected rats suppressed baseline PRL levels at 1 wk, but failed to significantly decrease PRL levels at 4, 7, 10, and 25 wk. Unlike NOM, bromocriptine, a direct DA agonist, strikingly reduced baseline PRL levels in EV-injected rats 1, 10, and 25 wk after the first EV injection. The administration of domperidone (DOM), a potent blocker of DA receptors, inconsistently increased plasma PRL at 1 wk and was ineffective at the following time intervals. Light and electron microscopic examinations of the hypothalamus revealed the existence in EV-injected rats of pathological changes in the arcuate nucleus region. In addition, measurement of DA in the median eminence of diluent- and EV-injected rats showed in the latter the presence of progressively reduced DA concentrations. These data suggest that rats with primary estrogen-induced PRL-secreting tumors have a defect in CNS-DA neurotransmission, a condition which has been postulated to also occur in human subjects bearing a prolactinoma. (43 Refs)

51. INDUCTION (OR STIMULATION) OF PROLACTIN AND GROWTH HORMONE PRODUCTION IN A RAT PITUITARY TUMOR CELL LINE BY BROMODEOXYURIDINE.

Cohen H, Andre J, Grenot C, Guillaumot P, Pascal O
Unite de Recherches Endocriniennes et Metabolliques, Chez l'Enfant, Hopital Debrousse, 29 rue Soeur Bouvier, 69322 Lyon Cedex 1, France
Endocrinology; 110(2):421-427 1982

Under basal conditions, a rat pituitary tumor cell line (C8 11RAP) does not secrete any detectable PRL, FSH, and LH, and secretes only minute amounts of GH (27.1 +-0.5 ng/10(6) cells/24 hr), as evaluated by RIA. Bromodeoxyuridine (BrdUrd) added to the culture medium induced the accumulation of PRL into cells and medium, increased that of GH, but did not induce that of LH or FSH. The amount of radioimmunoassayable PRL and GH accumulated in the medium increased after a lag period of 15 days and was drug concentration dependent. Maximal accumulation was 232.9 +-36.8 and 493.6 +-41.5 ng/10(6) cells/24 hr for PRL and GH, respectively, at 50 ug/ml BrdUrd. In the presence of BrdUrd (greater than or equal to 20 ug/ml), the cells grew more slowly and were more strongly attached to the flasks. All of the effects induced by BrdUrd were reversible. PRL and GH were characterized by three methods: (1) radiocompetition with increasing dilution of samples; (2) Sephadex chromatography, followed by RIAs; and (3) sodium dodecyl sulfate-polyacrylamide gel electrophoresis done on the immunoprecipitate of the proteins secreted by cells incubated with [3H]leucine. Chronic treatment with TRH (3 x 10(-6) M) of cells grown without BrdUrd was unable to increase the production of GH or to induce that of PRL. On the other hand, after the same treatment of cells cultured in the presence of BrdUrd, the amounts of PRL accumulated in the culture medium or cells were increased two- to seven-fold over unstimulated levels; under the same conditions, GH accumulation in the medium was also increased, but this augmentation was less than that of PRL. These results indicate that BrdUrd simultaneously induces or stimulates the production of PRL and GH in C8 11RAP cells, and that TRH increases the production of both hormones only in BrdUrd-treated cells. (Author abstract) (21 Refs)

52. HISTIDYL-PROLINE DIKETOPIPERAZINE SUPPRESSES PROLACTIN SECRETION IN HUMAN PITUITARY TUMOUR CELL CULTURES.

Melmed S, Carlson HE, Hershman JM
Dept. Medicine, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA
Clin Endocrinol (Oxf); 16(1):97-100 1982

Because histidyl-proline diketopiperazine (HPD), a metabolite of TRH, has been shown to suppress prolactin (PRL) release by rat pituitary tumor cells, human pituitary tumor cells were exposed to this compound. Monolayer cell cultures were initiated from pituitary tissue removed by transsphenoidal surgery from two patients with prolactin-secreting microadenomas. Tumor fragments were mechanically dispersed; cells were seeded into multiwell plates and incubated in Ham's F-10 medium enriched with fetal calf serum (20%). HPD (7.5 ng/ml) suppressed PRL release by both tumor cell cultures. Theophylline reversed the inhibition of PRL release induced by HPD. The data raise the possibility that HPD may act as an endogenous prolactin-inhibiting factor in man. (Author abstract) (7 Refs)

53. ESTABLISHMENT OF FUNCTIONAL HUMAN PITUITARY TUMOR CELL CULTURES.

Melmed S, Odenheimer D, Carlson HE, Hershman JM
Endocrine Res. Lab., Medical and Res. Services, Wadsworth Veterans Admin. Medical Center, Los Angeles, CA
In Vitro; 18(1):35-42 1982

Five primary human pituitary tumor cell cultures were initiated from adenoma fragments obtained from patients with prolactin-secreting adenomas and acromegaly. Functional cell cultures were maintained and propagated in monolayer or suspension culture for up to 9 mo. Optimal cell viability and growth were achieved using Ham's F10 medium enriched with 20% fetal bovine serum, although cells from a patient with acromegaly also grew in serum-free, defined, hormone-containing medium. Bromocriptine (100 ng/ml) did not alter the growth curve of replicating cells derived from a patient with acromegaly. These cells initially secreted 5.5 ug human growth hormone/10(6) cells, and hormone production diminished after 6 wk. Prolactin secretion by cells derived from prolactinomas (0.5 to 1.3 ug/10(6) cells/24 hr) was stimulated by thyrotropin-releasing hormone (10 ng/ml) in two of the cultures. Both dopamine (10 ng/ml) and nickel chloride (1 mM) suppressed PRL secretion. These studies demonstrate that responsive human pituitary tumor cell cultures can be initiated and maintained. (Author abstract) (26 Refs)

54. ANALYSIS OF REGIONAL CHANGES IN BRAIN SEROTONERGIC ACTIVITY ASSOCIATED WITH CANCER ANOREXIA (MEETING ABSTRACT).

von Meyenfeldt M, Chance WT, Fischer JE

Department of Surgery, University of Cincinnati, Medical Center, Cincinnati, OH

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

We have previously observed changes in CNS metabolism of serotonin (5-HT) within both the Walker (W) 256 and methylcholanthrene (MCA) induced sarcoma models of cancer anorexia. Therefore, we investigated regional brain changes in 5-HT, tryptophan (TRP) and 5-hydroxyindoleacetic acid (5-HIAA) associated with cancer anorexia induced by these two tumor lines. W 256 and MCA tumor-bearing (TB), pair-fed (PF) control and freely-feeding (FF) control rats were sacrificed after the development of anorexia, with the brains removed and dissected into cortex, corpus striatum, hippocampus, hypothalamus, diencephalon, mesencephalon, pons-medula and cerebellum prior to freezing in liquid nitrogen. Fluorometric assay indicated TRP to be elevated in diencephalon, mesencephalon, cortex, hypothalamus, corpus striatum and cerebellum of W 256 rats, while MCA rats exhibited increased TRP only in diencephalon and corpus striatum. Although W 256 rats showed increased levels of 5-HT only in diencephalon and cerebellum, MCA rats showed increased levels of 5-HT in all areas except hypothalamus and mesencephalon. Analysis of 5-HIAA indicated elevations in cortex, hippocampus, diencephalon, pons-medulla and cerebellum of W 256 rats, with MCA rats exhibiting increased 5-HIAA in all areas except the hypothalamus. The elevations of 5-HT and 5-HIAA in more areas within the MCA tumor line may reflect the more severe anorexia and cachexia of this model. Furthermore, the absence of changes in PF rats suggest that the increase in 5-HT activity does not merely result from nutritional deficits. (no Refs)

55. CORRELATION OF CHANGES IN BRAIN INDOLEAMINE METABOLISM WITH ONSET OF ANOREXIA IN RATS.

von Meyenfeldt M, Chance WT, Fischer JE

(c/o Fischer) Dept. Surgery, Univ. Cincinnati Medical Center, 231 Bethesda Ave., Cincinnati, OH, 45267

Am J Surg; 143(1):133-138 1982

The association of elevated brain serotonergic activity with cancer anorexia was investigated in three experiments. Significant increases in whole brain tryptophan, serotonin and 5-hydroxyindole acetic acid in anorectic rats bearing methylcholanthrene sarcomas demonstrated the general nature of this phenomenon. In the Walker 256 sarcoma model, significant increases in whole brain serotonin and 5-hydroxyindole acetic acid immediately preceded the onset of anorexia, suggesting that these changes in serotonin activity were not caused by decreased food intake. Investigations of regional brain changes in serotonin activity of rats bearing Walker 256 tumors revealed widespread increases in tryptophan, while serotonin was increased in the diencephalon and cerebellum and 5-hydroxyindole acetic acid was increased in the cortex, hippocampus, diencephalon, pons-medulla and cerebellum. Therefore, these experiments demonstrate that increased brain serotonin activity is a general phenomenon, being observed in two lines of anorexia-producing tumors, that it precedes the onset of anorexia and that selective increases in serotonin activity occur within different regions of the brain. (Author abstract) (19 Refs)

RECEPTOR/ BINDING SITES

56. PROLACTIN AND PROLACTIN RECEPTOR INTERACTIONS IN NORMAL AND NEOPLASTIC TISSUE.

Kelly PA, Djiane J, Turcot-Lemay L
Dept. Molecular Endocrinology, Le Centre Hospitalier de l'Universite Laval, Qubec G1V 4G2, Canada
Adv Exp Med Biol; 138:211-229 1982

Regulation of hormone receptors in nitroso-methylurea (NMU)-induced mammary tumors, the interaction of prolactin with prolactin receptors, and the down-regulation of prolactin receptors induced by prolactin both in vivo and in vitro are described. Prolactin receptors in NMU-induced tumors are reduced following ovariectomy of animals with newly formed tumors (2.5 mo after NMU injection) or in those animals with tumors present for longer periods. Prolactin receptors appear to have a relatively rapid turnover, based on the rate of receptor replenishment following removal of cycloheximide. (50 Refs)

57. IMMUNOCYTOCHEMICAL AND AUTORADIOGRAPHIC DEMONSTRATION OF PROLACTIN BINDING TO HUMAN BREAST CANCER CELLS IN TISSUE CULTURE.

Paterson JA, Salih H, Shiu RP
Dept. Anatomy, Univ. Manitoba, Winnipeg, Manitoba R3E 0W3, Canada
J Histochem Cytochem; 30(2):153-156 1982

Specific binding of human prolactin to human breast cancer cells in culture was demonstrated for the first time by immunocytochemistry and autoradiography. Using the former technique, it was found that prolactin binding to the cell surface was heterogeneous: some cells showing intense to moderate peroxidase reaction product and some cells showing absence of reaction product. After the cells were incubated with 125I-labeled prolactin and then embedded in plastic, autoradiography of sections revealed both surface-localized and intracellular silver grains, the latter suggesting internalization of prolactin. These two cytological techniques are useful for visualizing prolactin binding to human breast cancer cells and are applicable to studies on prolactin binding in human breast cancer. (Author abstract) (14 Refs)

58. HISTOLOGY AND CYTOMETRICS IN HUMAN BREAST CANCERS ASSAYED FOR THE PRESENCE OF PROLACTIN RECEPTORS.

Codegone ML, Di Carlo R, Muccioli G, Bussolati G
(c/o Bussolati), Istituto di Anatomia e Istologia Patologica, Via Santena 7, 10126 Torino, Italia
Tumori; 67(6):549-552 1981

Histology and cytometrics were evaluated in 50 cases of human breast infiltrating carcinomas (44 ductal, 6 lobular) assayed for the presence of prolactin receptors (PR). The tumors were considered PR positive when the level of specific binding reached or exceeded 0.5%. Twenty-six ductal infiltrating carcinomas and 4 lobular ones were PR positive. No strict correlation was found between PR and degree of histologic differentiation (expressed in grades) or menopausal status. Better differentiated (Grade I) ductal carcinomas were, however, mostly PR negative. Evaluation of the mean nuclear diameter (MND) and of the maximal epithelial cellularity (MEC) revealed that in ductal carcinomas a high level of PR (greater than 3% specific binding) was significantly correlated with a high MND. It is concluded that, contrary to that observed in estrogen receptor-positive tumors, PR-positive human ductal carcinomas are more likely to have large nuclei, ie, cytologically anaplastic, whereas better differentiated (Grade I) carcinomas are generally PR negative. (Author abstract) (15 Refs)

59. CLINICAL EVALUATION OF PROLACTIN RECEPTORS IN HUMAN BREAST CANCER TISSUES: STATISTICAL ANALYSIS OF 160 CASES (MEETING ABSTRACT).

Waseda N, Kato Y, Imura H, Kurata M

Department of Medicine, Kyoto University Facility of Medicine, Kyoto, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Specific receptors for prolactin (PRL-R) and estrogen (ER) were determined in 160 primary breast cancer tissues and relationship between receptors and clinical findings was statistically analyzed. PRL-R was positive in 15% and ER was detectable in 41% of them. Higher ER levels were found in obesity and in postmenopausal cases, whereas PRL-R was not correlated to menopause nor obesity. Recurrent rate was significantly higher in PRL-R positive group than others. Patients with both positive PRL-R and ER showed much higher recurrence. These results suggest a possible role of PRL in human breast cancer. (no Refs)

60. SIGNIFICANCE OF PROLACTIN RECEPTORS (PR) IN HUMAN BREAST CANCER. STATISTICAL ANALYSIS OF A SERIES OF 92 CASES (MEETING ABSTRACT).

Bonneterre J, Peyrat JP, Beuscart R, Cappelaere P, Demaille A

Center Oscar Lambret, Lille, France

UICC Conference on Clinical Oncology, October 28-31, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

PR were measured in breast cancer tissues from 92 patients (pts) without metastasis. Free receptors were calculated after incubation of membrane proteins with 125 I labelled human growth hormone (hGH) in the presence and absence of unlabelled ovine prolactin. Total receptors were measured by the same method after desaturation of occupied sites by incubation with 3 M MgCl2 for 5 min and then cold Tris HCl (buffer pH 7.6) containing 0.1% bovine serum albumin (BSA). Tumors were consider as positive when the specific binding was higher than 0.8%. Forty-six percent of tumors were positive for free receptors and 72 percent for total receptors. PR were not significantly associated with clinical (age, wt, obesity, hormonal status, number of pregnancies, previous hormonal or antimitotic treatment) and histological (differentiation, cellular density, histoprognostic grading, stroma, number of invaded axillary nodes) features. Total PR were positively correlated to estradiol and progesterone receptors levels. Free and total PR were not correlated to 17 beta estradiol, estrone and prolactin plasma levels but pts were too few (29 pts) in this preliminary study. The desaturation with MgCl2 allows to reveal the endogeneous prolactin - occupied sites and to increase the rate of positive PR. But it is too early to decide if PR levels give more information than steroid receptor for treatment and/or prognostic of human breast cancer. (no Refs)

61. INSULIN RECEPTORS ON HUMAN LYMPHOID LINES OF B-CELL ORIGIN.

Aman P, Lundin G, Hall K, Klein G
Dept. Tumor Biology, Karolinska Institut, S-104 01 Stockholm, Sweden

Cell Immunol; 65(2):307-316 1981

Human lymphoid lines derived from normal or neoplastic B cells were assayed for insulin binding. 125I-labeled insulin was allowed to bind to cells. Bound radioactivity which was inhibited with unlabeled insulin was regarded as specific binding. Among 46 lines tested, 43 bound more insulin than normal peripheral B lymphocytes. The majority of the lines resembled activated lymphocytes, with regard to their insulin binding. More mature cells represented by EBV-transformed lines of normal origin, bound more insulin than the less differentiated Burkitt lymphoma lines. However, even the latter bound significantly more insulin than peripheral blood lymphocytes. (Author abstract) (35 Refs)

62. DEMONSTRATION OF RECEPTORS FOR INSULIN AND INSULIN-LIKE GROWTH FACTORS ON SWARM RAT CHONDROSARCOMA CHONDROCYTES. EVIDENCE THAT INSULIN STIMULATES PROTEOGLYCAN SYNTHESIS THROUGH THE INSULIN RECEPTOR.

Foley TP, Nissley SP, Stevens RL, King GL, Hascall VC, Humbel RE, Short PA, Rechler MM
Children's Hosp. Pittsburgh, 125 DeSoto St., Pittsburgh, PA, 15213

J Biol Chem; 257(2):663-669 1982

The insulin-like growth factor, multiplication stimulating activity (MSA), and insulin were recently shown to stimulate proteoglycan synthesis in monolayer cultures of chondrocytes derived from the Swarm rat chondrosarcoma. Insulin produced significant stimulation at a concentration of less than 1 ng/ml, suggesting that insulin was acting through the insulin receptor rather than through a somatomedin receptor. In this paper we have shown that the insulin-like growth factors IGF-I and IGF-II also are potent stimulators of [35S]sulfate incorporation into macromolecules recovered from the medium and cell layer matrix of the chondrosarcoma chondrocytes. Proinsulin was 3% as potent as insulin in stimulating [35S]sulfate incorporation. We identified receptors for insulin and the insulin-like growth factors, MSA, IGF-I, and IGF-II. Insulin, at concentrations 1,000 times the concentration required to produce the biologic response, did not compete for binding of 125I-MSA-II-1 or of 125I-IGF-II and only partially competed for 125I-IGF-I binding. Anti-insulin receptor IgG stimulated proteoglycan synthesis and competed for 125I-insulin binding. Fab fragment prepared from anti-insulin receptor IgG completely blocked the stimulation of [35S]sulfate incorporation into macromolecules by insulin while only partially inhibiting the biologic response to insulin-like growth factors, MSA, IGF-I, and IGF-II. Similarly, the anti-insulin receptor IgG only partially inhibited the binding of 125I-IGF-I and 125I-IGF-II while completely blocking the binding of 125I-insulin. We conclude that insulin stimulates proteoglycan synthesis in the chondrosarcoma chondrocytes by acting through the insulin receptor, whereas the insulin-like growth factors probably act through their own receptors. (Author abstract) (41 Refs)

63. CHARACTERIZATION OF THE ALPHA1-ADRENERGIC RECEPTOR SUBTYPE IN A SMOOTH MUSCLE CELL LINE.

Cornett LE, Norris JS
Dept. Physiology-Biophysics, Univ. Arkansas Medical Sciences, Little Rock, AR, 72205

J Biol Chem; 257(2):694-697 1982

We have identified in the DDT1 smooth muscle cell line a [3H]dihydroergocryptine-binding site having the characteristics of an alpha1-adrenergic receptor. Specific binding of [3H]dihydroergocryptine to DDT1 cells grown either in monolayer or suspension culture was reversible, saturable, and of high affinity, and the binding site demonstrated stereoselectivity. [3H]Dihydroergocryptine dissociation constants of 1.4 +-0.2 nM and 1.4 +-0.3 nM were observed for suspension and monolayer cells, respectively. However, the concentration of binding sites in suspension-cultured cells (65,100 +-8,300 sites/cell) was significantly greater (p less than 0.001) than that found in monolayer cells (27,900 +-4,300 sites/cell). The order of agonist competition for the binding site was epinephrine (Ki = 0.92 +-0.32 uM) greater than or equal to norepinephrine (Ki = 2.2 +-1.0 uM) much greater than isoproterenol (Ki = 137 +-17 uM), consistent with an alpha-adrenergic interaction. Results of competition experiments with specific antagonists prazosin (alpha1-selective) or yohimbine (alpha2-selective) and a computer modeling technique indicated that the alpha-adrenergic receptor of the DDT1 cell was predominantly (greater than 95%) the alpha1-subtype. (Author abstract) (25 Refs)

OTHER RELATED STUDIES

64. GROWTH FACTORS PRODUCED BY MALIGNANT CELLS.

Keski-Oja J, Vaheri A
Suomen Akatemia, Helsingin yliopiston virusopin laitos, 00290 Helsinki 29, Finland

Duodecim; 97(17):1383-1393 1981

The growth of normal cells is carefully controlled mostly by hormones, by hormone-like growth factors (GFs) and by extracellular substances, while malignant cells are in certain respects autonomous, less influenced than normal cells by body fluids and GFs from in vitro cultures. They do not react typically with other cells and are less inhibited in growth density. The malignant cell has the capacity to secrete its own GFs, which can even affect the secreting cell itself. It is not known what other target cells this 'autocrinic' secretion may have, but normal cells in the immediate vicinity tend to be involved with them. Some tumor-derived phenotypes and growth patterns are augmented when added to normal cell cultures. Tumor cells also secrete proteolytic enzymes and vascular change accelerating factors, contributing in turn to invasive, expansive growth in vivo. A study of these 'metastasizing' factors is important both for understanding the mechanism of malignant growth and for clarifying related possibilities for diagnosis and treatment. Subjects discussed are the histological characteristics of malignancy, polypeptide GFs secreted by normal tissues, sarcoma GFs, the transforming GF of human tumors, malignant-growth accelerating factors derived from cancer cells, MSA-like GFs, NGF-like GFs of melanoma cells, and the GFs of hematopoietic cells. (50 Refs) (In FIN)

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CHARACTERIZATION OF NON-STEROID HORMONES IN EXPERIMENTAL AND IN VITRO SYSTEMS

1. THE IMMUNOCYTOCHEMICAL DETECTION OF PROTEIN HORMONES IN HUMAN PROSTATIC TISSUES.

Sibley PE, Harper ME, Peeling WB, Joyce BG, Griffiths K
Tenovus Inst. for Cancer Res., The Heath, Cardiff CF4 4XX, Wales
Prostate; 2(2):175-185 1981

Benign prostatic hyperplastic tissue was obtained from 13 patients, and immunocytochemical detection of four pituitary

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protein hormones was investigated. Luteinizing hormone (LH), follicle stimulating hormone (FSH), growth hormone (GH), and prolactin were measured. In all 13 specimens, a minimal amount of staining was observed when the LH antiserum was used in the immunocytochemical process. Diffuse staining was observed in both stromal and epithelial regions and an artefactual precipitate was found above the plane of the section, making it difficult to estimate the significance of the results. Staining attributable to FSH antiserum was observed in cytoplasm of epithelial cells lining acini and in their secretions. Most cystic acini were intensely stained, while only a proportion of the epithelium in glandular acini displayed immunoreactive FSH localization. Stromal areas were blank. With GH antiserum, staining was confined to stromal areas and the epithelium was predominantly unstained. Prolactin was localized intracellularly in most of the epithelial cells. These results are consistent with the internalization of fragments or whole protein hormone molecules in prostatic epithelium; their significance is unclear. (33 Refs)

2. PROOPIOLIPOMELANOCORTIN PEPTIDES IN NORMAL PITUITARY, PITUITARY TUMOR, AND PLASMA OF NORMAL AND CUSHING'S HORSES.

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Endocrinology; 110(3):941-954 1982

Using RIAs for six regions within proopiolipomelanocortin (proOLMC), gel filtration, and electrophoresis, we studied pituitary peptides in a normal horse and one with Cushing's disease caused by a pars intermedia adenoma. Almost all immunoreactive (IR) ACTH (78%) was 4,500 mol wt (4.5K) ACTH in normal pars distalis, but it was almost 100% corticotropin-like intermediate lobe peptide (CLIP) in normal pars intermedia. alphaMSH and betaMSH were found mainly in pars intermedia; equal concentrations of the betaMSH precursors, betalipotropin (betaLPH) and gammaLPH, were found in pars distalis. Most IR-beta-endorphin (IR-betaEND) was found as betaEND in pars intermedia, but roughly equal concentrations of betaEND and its precursor, betaLPH, were found in pars distalis. A 33K molecule containing IR-ACTH, IR-gamma3MSH, and IR-betaEND, presumed to be proOLMC, and a variety of 15-27K presumed biosynthetic intermediates were found in both normal pars distalis and pars intermedia. The pars intermedia adenoma causing Cushing's syndrome contained high IR-peptide concentrations. Several differences in precursors were noted, including the presence of three larger presumed precursors (38.5K, 47K, and 63K) that had both ACTH and betaEND immunoreactivities and both deletions and additions of 15-27K intermediates. The Cushing's horse's plasma peptides reflected tumor concentrations; 4.5K ACTH was modestly elevated, but the concentrations of CLIP, alphaMSH, betaMSH, gammaLPH, and betaEND were dramatically increased. About 20% of plasma IR-ACTH and 5% of IR-betaMSH and IR- betaEND were found as high mol wt forms. Normal processing of horse proOLMC appears to be similar to that in other species, but may be altered in pars intermedia tumors of horses with Cushing's disease, the plasma of which contains disproportionately increased concentrations of pars intermedia proOLMC peptides. (Author abstract) (51 Refs)

3. PITUITARY ADENOMAS WITH HYPERFUNCTION OF TSH. FREQUENCY, HISTOLOGICAL CLASSIFICATION, IMMUNOCYTOCHEMISTRY AND ULTRASTRUCTURE.

Saeger W, Ludecke DK

Abteilung fur Pathologie, Marienkrankenhauses Hamburg, Alfredstrasse 9, D-2000 Hamburg 76, W. Germany

Virchows Arch [Pathol Anat]; 394(3):255-267 1982

In a collection of 564 surgically removed pituitary adenomas, four cases were found to have had elevated TSH plasma levels. One of these tumors (case 1) could be classified as a highly differentiated mucoid TSH cell adenoma presenting histochemical reactions typical of, as well as electron microscopical features identical to, normal TSH cells. Immunoenzymatic studies failed to demonstrate TSH in the tumor cells. Two further adenomas (case 2 and 3) were similarly structured in many areas, but showed regions of poorer differentiation in which cells with distinct pleomorphism, irregular secretory granules, increased numbers of ribosomes and a well developed rough endoplasmic reticulum were present. In 10% of the tumor cells GH could be demonstrated immunoenzymatically, but there was no TSH. The fourth adenoma was an undifferentiated acidophilic adenoma showing pleomorphic cells having slight acidophil and partly mucoid granulations. The ultrastructure showed convoluted nuclei, increased numbers of free ribosomes as well as abundant rough endoplasmic reticulum and secretory granules which were different in size and number but distinctly of the TSH cell type. Immunoenzymatically, TSH was found in some cells, with GH in more cells. Endocrinologically, elevated levels of GH were measured in cases 2, 3 and 4 with LH being increased in case 1. Clinical and morphological correlations are discussed. (Author abstract) (39 Refs)

4. TSH AND TSH-SUBUNIT PRODUCTION BY HUMAN THYROTROPHIC TUMOUR CELLS IN MONOLAYER CULTURE.

Filetti S, Rapoport B, Aron DC, Greenspan FC, Wilson CB, Fraser W

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Acta Endocrinol (Copenh); 99(2):224-231 1982

Studies were performed on pituitary adenoma tissue obtained from a patient with hyperthyroidism secondary to inappropriate thyrotropin (TSH) secretion. This study, the first to examine secretory function of human thyrotropic tumor cells in vitro, confirms the disproportionate production of alpha-TSH by these tumors, even though this may not be apparent from the level of the alpha-subunit in serum. The data indicate that TSH secretion by thyrotroph tumor cells, at least from this particular patient, remains sensitive to TRH stimulation and dopamine inhibition, but insensitive to inhibition by T3. Not all TSH bioactivity is reflected by the immunoassayable TSH concentration, suggesting that the tumor may be producing variants of normal TSH that nevertheless retain biological activity. Finally, the data suggest that, at least in this particular tumor, TRH stimulation of TSH secretion is not mediated by cAMP as a second messenger. (28 Refs)

5. THE PATTERN OF ECTOPIC HORMONE PRODUCTION IN LUNG CANCER.

Bondy PK

West Haven Veterans Admin. Medical Center, West Haven, CT, 06516

Yale J Biol Med; 54(3):181-185 1981

Pulmonary cancers produce many hormonal polypeptides. There is a tumor-specific pattern to the appearance of abnormal adrenal function and inappropriate secretion of vasopressin, which are frequently found in small cell undifferentiated carcinoma but occur only very rarely, if at all, in squamous tumors. Humoral hypercalcemia, on the other hand, occurs almost entirely in squamous tumors and is rarely if ever seen in small cell or large cell tumors or in adenocarcinoma. In contrast, 'big ACTH' and beta lipotropin are found in the plasma and tumor extracts of lung cancers of all types. Calcitonin and the beta chain of human chorionic gonadotropin are also found in the plasma of a considerable portion of patients with all histological types of lung cancers. (Author abstract) (29 Refs)

6. PURIFICATION AND PARTIAL CHARACTERIZATION OF A PROTEIN FROM CANCER ASCITES FLUID WHICH STIMULATES THE RESORPTION OF BONE EXPLANTS IN VITRO.

Nimberg RB, Humphries DE, Lloyd WS, Wells H, Schmid K

Dept. Periodontology, Henry M. Goldman Sch. Graduate Dentistry, Boston, MA, 02118

J Biol Chem; 257(5):2477-2482 1982

A protein capable of stimulating bone resorption in vitro has been purified approximately 1,250-fold from cancer ascites fluid. Purification was accomplished employing successive fractionation with ammonium sulfate, ion exchange, and Cibacron blue affinity chromatography, isoelectric focusing, and selective adsorption on hydroxylapatite. The bone-resorptive protein obtained by this procedure appeared homogeneous in polyacrylamide gels at pH 9.5, migrating with the mobility of an alpha2-globulin, and in sodium dodecyl sulfate polyacrylamide gels from which an apparent mol wt of 43,000 was calculated. The amino acid composition of the bone-resorptive protein distinguished itself by the absence of methionine and by its relatively high content of glycine (17%) and proline (11%). Furthermore, the protein possesses a single NH2-terminal amino acid residue (glycine). The ascites protein was found to contain 19% carbohydrate by weight including a high content of sialic acid (15 residues/mol) as compared to the other sugars (27 residues/mol). As to its biological properties, the homogeneous ascites glycoprotein proved to be as potent as parathyroid hormone in its ability to stimulate bone resorption in vitro. (Author abstract) (31 Refs)

7. GENERATION OF A MONOCLONAL ANTIBODY AGAINST FACTEUR THYMIQUE SERIQUE (FTS).

Ohga K, Incefy GS, Wang CY, Good RA

Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

Clin Exp Immunol; 47(3):725-734 1982

A monoclonal antibody against one of the thymic hormones, facteur thymique serique (FTS), was generated by hybridization between mouse NS-1 myeloma cells and BALB/c splenocytes, the latter obtained from BALB/c mice immunized with synthetic FTS coupled to mouse IgG. Enzyme-linked immunosorbent assay (ELISA) was developed and employed to detect the hybridoma secreting specific antibody. The monoclonal antibody (MA-FTS) was highly specific for FTS and did not cross-react with other thymic hormones or other unrelated peptides. MA-FTS could recognize FTS (or FTS-like molecule) in human serum and could absorb completely the FTS-like activity from human serum. (Author abstract) (25 Refs)

8. SOMATOSTATIN-28 ENCODED IN A CLONED CDNA OBTAINED FROM A RAT MEDULLARY THYROID CARCINOMA.

Goodman RH, Jacobs JW, Dee PC, Habener JF

Lab. Molecular Endocrinology, Massachusetts General Hosp., Boston, MA, 02114

J Biol Chem; 257(3):1156-1159 1982

We have constructed and cloned in bacteria complementary DNAs derived from a transplantable rat medullary thyroid carcinoma. Using a hybridization probe encoding an anglerfish islet pre-prosomatostatin, a precursor of the tetradecapeptide somatostatin, we have identified and isolated a clone containing a 400-base pair complementary DNA encoding most of the rat carcinoma pre-prosomatostatin. The amino acid sequence of the tetradecapeptide somatostatin and of the amino-terminally extended form, somatostatin-28 was deduced from the nucleotide sequence of the complementary DNA. Somatostatin-28 was found at the COOH terminus of a polypeptide of at least 80 amino acids indicating that somatostatin-28 arises by cleavage from a large precursor. The sequences of somatostatin-28 and somatostatin-14 are strictly conserved between the rat and other mammals. Such conservation of these sequences indicates strong selective pressures during evolution to maintain the sequence and suggests that somatostatin-28 may serve some essential biologic functions apart from, or in addition to, the important regulatory actions of somatostatin-14. Additionally, we found a high degree of homology in the amino acid sequences of the NH2-terminal extension peptides in the anglerfish islet and the rat carcinoma pre-prosomatostatins pointing further to a possible biologic function of these extension peptides. (Author abstract) (39 Refs)

9. THE BIOCHEMICAL PROPERTIES OF URINARY HUMAN CHORIONIC GONADOTROPIN FROM THE PATIENTS WITH TROPHOBLASTIC DISEASES.

Nishimura R, Endo Y, Tanabe K, Ashitaka Y, Tojo S

Dept. Obstetrics and Gynecology, Kobe Univ. Sch. Medicine, Kobe 650, Japan

J Endocrinol Invest; 4(3):349-358 1981

Human chorionic gonadotropin (hCG) was extracted from urine of a 23-yr-old woman with a hydatidiform mole, a 37-yr-old woman with metastatic choriocarcinoma, and a woman with a normal pregnancy by the standard kaolin-acetate method in conjunction with alcohol precipitation. Purification by diethylaminoethyl-cellulose chromatography and Sephadex G-100 gel filtration was followed by determination of amino acids, carbohydrates, and monosaccharides, sodium dodecyl sulfate polyacrylamide gel electrophoresis, 125I-hCG radioimmunoassay, 125I-hCG uptake in rats, and bioassay by ovarian wt method. Amino acid compositions of the three hCG samples were virtually identical. All three types of hCG could be separated into alpha and beta components by electrophoresis. They were similar in cross reactivities in terms of parallel dose response and dose inhibition to each other in hCG, alpha, and beta-subunits radioimmunoassays. The sialic acid content of hCG from the choriocarcinoma patient was undetectable, whereas the other two hCGs had about 8.5% sialic acid. Ovarian uptake of 125-hCG from the choriocarcinoma patient was approx 10% of the uptakes of the other two 125-hCG types, and agrees with low biological activity determined by the rat ovarian wt assay. Neoplastic or malignant transformation of trophoblasts may alter glycosylation, especially sialylation. (46 Refs)

10. CAPACITY FOR AMINE-PRECURSOR UPTAKE AND DECARBOXYLATION OF ARGYROPHIL CELL ADENOCARCINOMA OF THE ENDOMETRIUM.

Inoue M, Ueda G, Yamasaki M, Tanaka Y, Hiramatsu K, Sakumoto T, Kurachi K, Maeyama K, Yamatodani A
Dept. Obstetrics and Gynecology, Osaka Univ. Medical Sch., Osaka, Japan
Gynecol Oncol; 13(1):19-25 1982

The capacity for amine-precursor uptake and decarboxylation of the argyrophil cell adenocarcinoma of the endometrium was examined by fluorescence microscopy, microspectrofluorometry, and biochemical analyses. Both an argyrophil cell adenocarcinoma and a non-argyrophil cell adenocarcinoma of the human endometrium have been grown serially in nude mice. The nude mouse with the argyrophil tumor was injected intraperitoneally with amine precursor (3 mg of L-dopa) when the tumor attained a diameter of 2 cm. The nude mouse with the non-argyrophil tumor which had been injected with L-dopa and the one with the argyrophil tumor which had been injected with saline served as controls. With the use of the wet-histofluorescence method, intense green and yellow fluorescence was demonstrated in the cytoplasm of some cells of the argyr ophil cell adenocarcinoma transplanted to the nude mouse and injected with L-dopa, but none was observed in the controls. Microspectrofluorometrical and biochemical analyses strongly suggested that the fluorescent products were dopamine which was produced by decarboxylation of L-dopa. (Author abstract) (12 Refs)

CLINICAL, DIAGNOSTIC AND PROGNOSTIC STUDIES

11. DYNAMIC TESTS OF PROLACTIN SECRETION IN HYPERPROLACTINEMIC STATES: CARBIDOPA-L-DOPA AND INDIRECTLY ACTING DOPAMINE AGONISTS.

Genazzani AR, De Leo V, Murru S, Cocchi D, Camanni F, Muller EE (c/o Muller) Dept. Pharmacology, Univ. Milan, Via Vanvitelli, 32-20129 Milan, Italy
J Clin Endocrinol Metab; 54(2):429-435 1982

In normal subjects, similar degrees of PRL suppression have been reported after L-dopa alone and after a lower dose of L-dopa given in combination with carbidopa (CD), a peripheral inhibitor of L-dopa decarboxylase. In patients bearing PRL-secreting pituitary adenomas, CD-L-dopa induces a minimal suppression of plasma PRL, which is significantly less than after L-dopa alone. Similarly, indirectly acting dopamine (DA) agonists (IADAs), while capable of suppressing plasma PRL in normal subjects and subjects with puerperal hyperprolactinemia, fail to do so in patients with PRL-secreting adenomas. In the present study, to determine whether in puerperal subjects CNS dopaminergic function is actually preserved an to elucidate the mechanisms underlying the defective CNS dopaminergic function of patients with prolactinomas, we have investigated: (1) whether CD-L-dopa suppresses PRL levels in postpartum women; and (2) the PRL-inhibiting properties of two IADAs, viz nomifensine (Nom) and methylphenidate (Methphen), L-dopa alone, and L-dopa with CD-L-dopa in patients bearing PRL-secreting pituitary adenomas. The data indicate that (1) CNS dopaminergic function, as assessed by CD-L-dopa, is preserved in postpartum women; (2) there are patients bearing PRL-secreting pituitary adenomas who are unresponsive to the PRL-inhibiting properties of IADA, but suppress baseline PRL levels after CD-L-dopa in the same way as normal and postpartum subjects; and (3) IADAs and CD-L-dopa do not probe the same aspects of CNS dopaminergic function. (Author abstract) (23 Refs)

12. THE EFFECT OF NOMIFENSINE ON PROLACTIN SECRETION IN PATIENTS WITH SUSPECTED PITUITARY MICROADENOMA.

Jeske W, Stopinska U
Klinika Endokrynologii, CMKP, ul. Ceglowska 80, 01-809 Warszawa, Poland
Endokrynol Pol; 32(1):17-24 1981

Use of a new prolactin (PRL)-inhibition test was evaluated in 20 hyperprolactinemic female patients (20-40 yr old; 11 with galactorrhea and amenorrhea, 9 with oligomenorrhea and/or sterility) with no signs of pituitary adenoma on routine sellar x-ray. Blood samples for PRL estimation were collected at 0, 60, and 120 min after administration of 10 mg metoclopramide (MCP) po and at 0, 60, 120, 180, and 300 min after administration of 100 mg nomifensine (NFS) po. In 11 patients not responding to MCP, the bromocriptine (BCR) inhibition test was performed for comparison; PRL was measured at 0, 60, 120, and 180 min after administration of 2.5 (or 1.25) mg parlodel. Baseline PRL levels were elevated in all patients; three patients on NFS test and one on MCP test had normal basal PRL levels. No significant decrease in serum PRL was observed in patients not responding to MCP after NFS administration; max inhibition was 15%, but elevated PRL levels were observed in three patients. Administration of NFS was followed by an approx 50% reduction of PRL at 120-300 min in patients with normal or exaggerated response to MCP. BCR administration caused a marked decrease in PRL levels in eight patients, no change in one, and increased PRL levels in two patients. No side-effects were observed after administration of MCP or NFS; BCR caused postural hypotension in six patients. Results suggest that the NFS-inhibition and MCP-stimulation tests could be useful in diagnosis of pathological hyperprolactinemia. (17 Refs)

13. RESTORATION OF OVARIAN FUNCTION BY LOW NOCTURNAL SINGLE DAILY DOSES OF BROMOCRIPTINE IN PATIENTS WITH THE GALACTORRHEA-AMENORRHEA SYNDROME.

de Bernal M, De Villamizar M
Departamento de Medicina Interna, Universidad del Valle, Apartado Aereo 2188, Cali, Colombia
Fertil Steril; 37(3):392-396 1982

Eighteen hyperprolactinemic patients with either amenorrhea or both galactorrhea and amenorrhea were treated with 2.5 mg of bromocriptine per day supplied at night. Ovulation occurred in 16 patients, and 8 wishing to conceive became pregnant. One of these patients became pregnant for a second time at a bromocriptine dose as low as 1.25 mg/day. Normal ovulatory cycles in four women receiving 2.5 mg of bromocriptine per day could also be maintained at 1.25 mg, despite the differences in the degree of prolactin (PRL) inhibition. Progesterone and luteinizing hormone levels measured for both bromocriptine levels were consistent with ovulatory cycles. The low, single dose of bromocriptine per day supplied at night decreased PRL levels, but normalization of blood levels did not always occur. Eighty percent of the patients ovulated with prolactin values over 25 ng/ml (normal value = less than 20 ng/ml). (Author abstract) (18 Refs)

14. HYPERPROLACTINAEMIA IN MEN - RESPONSE TO BROMOCRIPTINE THERAPY.

Prescott RW, Kendall-Taylor P, Hall K, Johnston DG, Crombie A, McGregor A, Hall R

Dept. Medicine, Univ. Newcastle upon Tyne, Newcastle upon Tyne NE1 4LP, England

Lancet; 1(8266):245-249 1982

Men with hyperprolactinemia present with large tumors. Conventional therapy with surgery and/or irradiation is unsatisfactory, with up to 100% of patients remaining hyperprolactinemic (or subsequently developing pituitary insufficiency). In view of reports of bromocriptine-induced regression of prolactinomas, eight consecutive male hyperprolactinemic patients with impotence and/or symptoms related to local tumor effects were treated with bromocriptine 20 mg daily as sole therapy for 3-11 mo. Symptoms were relieved partly or completely in seven patients and serum prolactin was restored to normal or near normal in all men. Serum thyroxine and plasma cortisol response to hypoglycemia became normal in two men who had subnormal values before therapy. Mean serum growth hormone response to hypoglycemia rose significantly as did plasma testosterone concentrations. Evidence of tumor regression, sometimes massive, was seen in the six patients who underwent repeat radiology. The symptomatic relief and biochemical and radiological improvement in these patients indicate that bromocriptine therapy may now be the treatment of choice for hyperprolactinemic men with large tumors. (Author abstract) (37 Refs)

15. HYPOTHALAMIC-PITUITARY-TESTICULAR FUNCTION IN MEN WITH PRL-SECRETING TUMORS.

Ambrosi B, Gaggin M, Travaglini P, Moriondo P, Elli R, Faglia G

Clinica Medica 2, Unita Endocrina, Pad. Sacco, via F. Storza 35, 20122 Milano, Italy

J Endocrinol Invest; 4(3):309-315 1981

Levels of serum prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), and 17 beta estradiol (E2) were determined in 33 men (16-64-yr-old; mean 42 yr) with PRL-secreting tumors. Patients with signs of Cushing's disease, Nelson's syndrome, or acromegaly were excluded. Hormone levels were determined before and after administration of human chorionic gonadotropin (hCG: 5,000 im for 3 days), gonadotropin-releasing hormone (GnRH: 100 ug iv), clomiphene citrate (CC: 100 mg/day for 5 days), and metoclopramide (MC: 20 mg iv) to selected groups of patients. Mean increase in T level was significantly less in the 14 patients tested than in normal adult men; serum T increase was correlated with FSH levels, but not with those of LH and PRL, and serum E2 increase after treatment was significantly lower in patients than controls. GnRH administration to 29 patients caused a mean LH increase significantly less than that in normal men. Of the hyperprolactinemic men given CC, 6/10 exhibited a normal response, 1/10 showed an impaired response, and 3/10 did not respond; serum T and E2 increases were also significantly lower. MC did not elicit a significant increase in LH either in those with prolactinemia or in normal subjects; PR did not rise in hyperprolactinemic men but did increase significantly in controls. Excess PRL apparently plays an inhibitory role in the hypothalamic-pituitary-testicular axis that seems to be related to the degree and duration of hyperprolactinemia. (27 Refs)

16. CYPROTERONE ACETATE, TESTOSTERONE, LH, FSH, AND PROLACTIN LEVELS IN PLASMA AFTER INTRAMUSCULAR APPLICATION OF CYPROTERONE ACETATE IN PATIENTS WITH PROSTATIC CANCER.

Rost A, Schmidt-Gollwitzer M, Hantelmann W, Brosig W
Dept. Urology, Klinikum Steglitz, Free Univ. Berlin, Hindenburgdamm 30, D-1000 Berlin 45, W. Germany
Prostate; 2(3):315-322 1981

Five men with prostatic carcinoma (stages T3N0M0) received cyproterone acetate (Androcur-Depot:CPA: 300 mg im, weekly) and levels of plasma CPA, testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin were determined by radioimmunoassay after the first, third, and fifth injections. CPA levels were slightly higher after the fifth injection than after earlier injections, suggesting a balance in release from the depot and excretion. Testosterone values were reduced after the first injection and stabilized at a lower level after subsequent injections. LH and FSH were slightly diminished after each injection, whereas prolactin levels were increased. (28 Refs)

17. PROLACTIN - AN IMPORTANT HORMONE IN BREAST NEOPLASIA?

Henderson BE, Pike MC, Moon RC, Segaloff A, Bulbrook RD, Meites J, Siiteri PK, Shellbarger CJ, Cole P
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep; 8:115-130 1981

The role of prolactin in the development and growth of breast tumors is discussed. After the first full-term pregnancy, a woman's plasma prolactin level may be permanently lowered, perhaps providing protection against the development of breast cancer. Breast cancer patients and their high-risk family members generally have elevated prolactin levels. Prolactin level has not been correlated with wt or any dietary nutrients. Prolactin may enhance the mitogenic effect of estrogen. (30 Refs)

18. ENDOCRINE MATURATION IN THE COURSE OF FEMALE PUBERTY.

Vihko R, Apter D, Siiteri, Henderson BE
Dept. Clinical Chemistry, Univ. Oulu, SF-90220 Oulu, 22, Finland
Banbury Rep; 8:57-69 1981

Results of studies related to changes in levels of serum peptide (ACTH, follicle-stimulating hormone, luteinizing hormone, and prolactin), steroids (pregnenolone, progesterone, 17-hydroxyprogesterone, cortisol, dehydroepiandrosterone, androstenedione, testosterone, 5-alpha-dihydrotestosterone, androsterone, and estradiol), and hormone concentrations in girls at puberty, are presented. The results are focusing on hormonal changes associated with the appearance of menarche and the maturation of the menstrual cycle. (29 Refs)

19. ENDOCRINOLOGICAL STUDIES OF PATIENTS AFTER SURGERY IN THE PITUITARY AREA(I).

Dolecek R, Zavada M
Department of Medicine, Regional Hospital, Ostrava, Czechoslovakia
Srp Arh Celok Lek; 109(2):197-215 1981

Ninety-four patients (61 men and 33 women; 15-73 yr old) had surgery in the pituitary area due to chromophobe adenoma (60), acromegaly (16), craniopharyngeoma (CP: 8), and others (10). Sixty three patients were studied after surgery, and 31 before and after. The study lasted 15 yr and the patients came 2-3 times a yr for follow-up. Endocrinologic tests included 17-ketosteroids (17-KS) and 17-ketogenic steroids (17-KGS) with metyrapone in urine; follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), thyroid releasing hormone (TRH), prolactin (PRL), and testosterone (TE), in plasma or serum. Except for some patients sustaining damage of vital areas, the patients were well, when receiving regular substitution therapy, and many of them returned to work. Values of 17-KS and 17-KGS were decreased. TE values in men were low, even very low, often without correlation with LH values. FSH values were a better indicator of the patients condition than LH values, although both were lower after surgery. On the contrary TRH values were not reduced in most of the patients, however, they were absent in some of them. Most pronounced changes were observed in CP patients. Activities of peripheral glands were often low even in some patients with normal levels of protein hormones. Changes in the endocrine status were observed with the passage of time, in some patients partial improvement of some hormone values was noted. (2 Refs) (In SCC)

20. ENLARGEMENT OF THE SELLA TURCICA IN SOME PATIENTS WITH LONGSTANDING UNTREATED ENDEMIC CRETINISM. SERUM TSH, ALPHA, TSH-BETA, AND PROLACTIN RESPONSES TO TRH.

Medeiros-Neto GA, Kourides IA, Almeida F, Gomes E, Cavaliere H, Ingbar SH
Hospital das Clinicas, C. Postal 8091, 01000 Sao Paulo, Brazil
J Endocrinol Invest; 4(3):303-307 1981

Serum levels of thyroid hormone, thyroid-stimulating hormone (TSH), alpha and TSH-beta, and prolactin pituitary reserve were measured by radioimmunoassay, and the size of the sella turcica was determined using lateral skull films, in 27 patients from an isolated Central Brazilian village where severe Iodine deficiency exists. Responses to thyrotropin releasing hormone administration (200 ug iv) are described. Endemic and neurologic cretinisms was compared, and hormone levels are discussed in relation to literature reports of cases of TSH-secreting pituitary tumors. (15 Refs)

21. CIRCADIAN ASPECTS OF SERUM PROLACTIN AND TSH LOWERING BY BROMOCRIPTINE IN PATIENTS WITH PROSTATIC HYPERTROPHY.

Tarquini B, Halberg F, Seal US, Benvenuti M, Cagnoni M
(c/o Seal), Veterans Admin. Hosp., Building 29, Room 207, Minneapolis, MN, 55417
Prostate; 2(3):269-279 1981

Nineteen patients (59-84 yr old) with benign prostatic hypertrophy were divided into four groups and treated with bromocriptine mesylate (BCM: 2.5 mg po) at 1, 7, 13, and 19 hr after awaken ing (HAA), which corresponded to 6 am, noon, 6 pm and midnight, local time. Groups were tested in October, November January, and March. BCM decreased serum prolactin at three of the four test times. for thyroid stimulating hormone (TSH) there was a decrease following BCM administration at 13 and 19 HAA. Furthermore, a circannual rhythm of both prolactin and TSH levels was demonstrated, but could not be statistically controlled due to study duration (5 mo). Confusing results of previous work may be explained by lack of correction for natural rhythms of prostatic hormone levels; future work must control for both circadian and circannual rhythms. (27 Refs)

22. GYNECOMASTIA IN MEN FOLLOWING ANTINEOPLASTIC THERAPY.

Trump DL, Pavy MD, Staal S
Wisconsin Clinical Cancer Center, K4/642 Clinical Science Center, 600 Highland Ave., Madison, WI, 53792
Arch Intern Med; 142(3):511-513 1982

Six men had painful gynecomastia develop during or following the administration of cytotoxic chemotherapy. Alternative causes of gynecomastia were not delineated in any patient. Sharp increases in levels of plasma follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were noted in five patients. Plasma testosterone concentrations were within or above the normal range in all five patients in whom they were determined. In three patients, plasma estradiol concentrations were modestly increased. One patient was studied prospectively: painful gynecomastia developed at a time when plasma FSH and LH levels were elevated, serum testosterone was decreasing from supranormal to low-normal concentrations, and plasma estradiol was rising to high levels. Plasma prolactin levels were increased in one of four patients in whom they were measured. The mechanisms leading to gynecomastia following cytotoxic chemotherapy were not defined. Damage to germinal epithelium and Leydig cells as well as changes in the peripheral metabolism of testosterone and estrogen may be important. Gynecomastia may occur following cytotoxic chemotherapy and does not necessarily represent recurrent or progressive cancer. (Author abstract) (24 Refs)

23. HORMONAL CHANGES IN PATIENTS WITH PRECANCER AND CANCER OF THE ENDOMETRIUM.

Griaznova IM, Kovrizhina LP
Dept. Obstetrics and Gynecology, N. I. Pirogov Second Medical Inst., Moscow, USSR
Akush Ginekol (Mosk); (12):20-23 1981

The state of the hypophyseal-ovarian system was studied in 150 patients with endometrial hyperplasia and in 60 patients with endometrial cancer. Comparative analysis of the types of hyperplastic processes showed that glandular-cystic hyperplasia and endometrial polyposis were dominant in the premenopausal women (78.6% and 42.9%, respectively), while glandular and glandular-fibrous polyps were dominant in the postmenopausal women (66.7% and 63.6%, respectively). All patients with hyperplastic processes showed significant decrease of the level of follicle-stimulating hormone and increase of the level of prolactin. The premenopausal patients with endometrial cancer showed 4x increase of the level of the luteinizing hormone and 2x increase of the estradiol level, compared with healthy controls. Decrease of the somatotropin level was observed in 70% of the patients with endometrial cancer. (13 Refs) (In RUS)

24. FEEDBACK CONTROL OF LUTEINIZING HORMONE AND FOLLICLE-STIMULATING HORMONE SECRETION BY TESTOSTERONE AND ESTRADIOL IN MEN: PHYSIOLOGIC AND CLINICAL IMPLICATIONS.

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Dept. Medicine, Div. Endocrinology, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033
Clin Biochem; 14(5):243-251 1981

Physiology of the hypothalamic-pituitary-testicular axis (HPTA), clinical application of physiologic principles, clinical disorders of HPTA, diagnosis and treatment of reproductive disorders in men, and new perspectives are reviewed. Differential diagnosis of hypogonatotropic hypogonadism includes diagnosis of hypothalmic and pituitary tumors and functional and anatomic disorders caused by the tumors. (18 Refs)

25. CORTISOL SUPPRESSION TEST IN PATIENTS WITH ELEVATED ADRENOCORTICOTROPIC HORMONE LEVELS.

Koletsky RJ, Dluhy RG, Crantz FR, Williams GH

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Ann Intern Med; 96(3):277-280 1982

Increased adrenocorticotropic hormone (ACTH) levels after bilateral adrenalectomy could be secondary to a pituitary tumor, under replacement with cortisol, or an abnormality in the hypothalmic-pituitary-adrenal feedback loop. To distinguish between these possibilities, ACTH levels were measured before and after cortisol infusion (20 mg/h for 4 hr) in five groups: normal volunteers; patients with idiopathic adrenal insufficiency; and with bilateral adrenalectomy for Cushing's syndrome with no roentgenographic evidence of pituitary tumor, with pituitary tumors, and with equivocal roentgenographic studies (suspect pituitary tumors). Control ACTH levels in all groups of patients were higher than in normal volunteers, but there was overlapping. Cortisol infusion suppressed ACTH in all subjects, but the reductions in the last two groups were less than in the first three. The cortisol suppression test appears to be useful in determining whether increased ACTH level after adrenalectomy is due to a pituitary tumor. (Author abstract) (12 Refs)

26. RADIOIMMUNOLOGICAL HORMONE DETERMINATIONS AND ADRENAL CORTEX SCINTIGRAPHY IN THE DIFFERENTIAL DIAGNOSIS OF ADRENOCORTICAL TUMORS.

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Kiewer Forschngsinstitut fur Endokrinologie und Stoffwechsel, Ministerium fur Gesundheitswesen der UkrSSR, ul. Vysgorodskaja, 69, 252114, Kiew, USSR

Radiol Diagn (Berl); 22(6):806-814 1981

Scintigraphic and hormonal indicators of adrenocortical tumors and diseases of the hypothalamic-hypophyseal-suprarenal (HHS) system were studied in 68 patients (17-57 yr old). Diagnosis was based on clinical, radiological, and laboratory findings. Basal ACTH, cortisol, aldosterone, and renin activities were measured in venous blood of peripheral, renal, and adrenal veins and the inferior vena cava. Daily fluctuations in hormonal levels and fluctuations caused by stress induced by insulin-hypoglycemia or ACTH administration were measured. Differences in measured values allowed differentiation of Itsenko-Cushing's syndrome, Cushing's disease, Conn's syndrome, hypertension, malignant hypertonia, and secondary aldosteronism. Differences reflected differing organic basis for these diseases. Adrenocortical tumors were characterized in scintigraphy by enlargement of the involved adrenal gland with intense accumulation of 131I-19-iodocholesterol. Results indicate that nuclear medical methods are suitable for differential diagnosis of hormonally active tumors and diseases of the HHS system and for monitoring the course of treatment. (9 Refs) (In GER)

27. TREATMENT OF ACROMEGALY BY TRANS-SPHENOIDAL OPERATION, 90-YTTRIUM IMPLANTATION AND BROMOCRIPTINE: RESULTS IN 230 PATIENTS.

Quabbe HJ, Buch K, Solbach HG, Wiegelmann W, Benker G, WindeckR, Allhoff PH, Kobberling J, Mayer G, Ludecke DK, SchraderD, Lucke C, Wagner TO, Winkelmann W, Heesen D, Wilcke O, von Werder K, Fahlbusch R

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Clin Endocrinol (Oxf); 16(2):107-119 1982

Two hundred and thirty patients with acromegaly were diagnosed and treated in a prospective cooperative study in 12 university clinics. Primary treatment was: trans-sphenoidal surgery (152 patients), trans-sphenoidal surgery with additional cryotherapy (18 patients), Yttrium-90-implantation (30 patients), bromocriptine (30 patients). The results of endocrine assessment before treatment and 6 mo after operation, 90-Y implantation or commencement of bromocriptine therapy are reported. The best results (low GH, no or little deterioration of pituitary function, low complication rate) were achieved by trans-sphenoidal surgery, especially in patients with intrasellar tumors (basal GH less than 5 ng/ml in 59.7%). Results were less good with increasing tumor size. Additional cryosurgery was accompanied by a high rate of anterior pituitary insufficiency and is no longer employed. Yttrium-90-implantation resulted in less improvement in GH levels (basal GH less than 5 ng/ml in 51.7% of patients with intrasellar tumors), a high rate of pituitary insufficiency and more complications. Bromocriptine treatment was least effective in lowering GH concentrations (basal GH less than 5 ng/ml in 33% of patients with intrasellar tumors). Different criteria for treatment success were compared. In the entire group, basal GH concentrations below 5 ng/ml were attained in 51.7% of all patients whose values were higher than this prior to treatment. Suppressibility of GH below 2 ng/ml during glucose loading occurred in only 34.9%. An abnormal GH response to TRH/LHRH was present in 47.2% before and in 43.4% after/during treatment. The prognostic significance of this latter finding must be evaluated by further study. (Author abstract) (32 Refs)

28. HISTAMINE AND SEROTONIN LEVELS IN PATIENTS WITH BILIARY TRACT DISEASES BEFORE AND AFTER SURGERY.

Kolesova OE, Nisimov EB, Evdokimov EA, Vasil'ev IT

Central Inst. Advanced Training for Physicians, Moscow, USSR

Klin Med (Mosk); 59(12):76-79 1981

The blood levels of histamine (HA) and serotonin (ST) were studied in 30 patients (13 men, 17 women; 38-60 yr old) with various diseases of the biliary tract. Of these patients, 15 had cholecystitis and 15 had obstructive jaundice due to cholelithiasis or pancreatobiliary neoplasms. Prior to surgery, all patients showed increase of HA and ST levels. Surgery resulted in gradual normalization of HA and ST levels: the patients with cholecystitis showed more rapid recovery of HA and ST levels than the patients with obstructive jaundice. (13 Refs) (In RUS)

29. ALTERATIONS IN THYROID HORMONE METABOLISM DURING CHEMOTHERAPY IN PATIENTS WITH TESTICULAR CARCINOMA.

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Clin Endocrinol (Oxf); 16(3):303-313 1982

In a prospective study, the effects of chemotherapy on thyroid function in patients with non-seminoma testicular carcinoma were evaluated. Thirty-one patients were studied; in 16 immunoassayable HCG was present, but altered thyroid function could not be established. In 15 patients an exaggerated TSH response to TRH was observed. In these patients, although T3 and T4N values were normal, basal TSH levels were higher compared to patients with a normal TSH response, probably due to preceding lymphangiography. During chemotherapy, T4N, T3 and rT3 levels rose significantly, but basal TSH levels and the TSH response to TRH decreased. In contrast, the prolactin responses to TRH increased. The observed changes in thyroid function during chemotherapy appear to result from delayed thyroid hormone clearance, probably caused by an effect of chemotherapy on deiodinating enzyme activity. This would result, in an increase in T4N and rT3 levels and a fall in TSH levels and in the TSH response to TRH. Furthermore, after therapy the raised T4N and lowered TSH levels remained, whilst the FT3 level did not change either during or after therapy, suggesting an unaltered hypothalamic/pituitary axis. (Author abstract) (43 Refs)

30. THYROID MALIGNANCY IN THE ELDERLY.

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Geriatrics; 37(3):119-121,124-125 1982

Pathogenesis, diagnosis, therapy, follow-up care, complications, and prognosis of thyroid malignancy (TM) in the elderly are described. Patients with follicular and anaplastic tumors (approx 50%) and with papillary cancers (approx 33%) gave a history of a goiter that had been unchanged for many yr but had grown recently. The most common clinical manifestation is a mass in the lower neck or enlargement of a preexisting goiter. Radioiodine scanning, ultrasonography, and fine needle aspiration are performed Patients with clinically evident cancers require a search for metastases, using chest x-ray, bone scan, or skeletal x-rays, liver function tests, and liver and brain scan. Surgery is indicated in almost all patients. Radioiodine is important in treatment of papillary and follicular thyroid cancers. External radiation may play a vital role for every type of TM. Thyroid hormone should be administered to inhibit thyroid-stimulating hormone release and to provide replacement therapy where the disease or the treatment left insufficient thyroid tissue to maintain the euthyroid state. Complications include spinal cord compression caused by an extradural tumor originating in a vertebral body and surgical complications that may occur with any thyroid operation. Pulmonary fibrosis and spinal cord necrosis are serious complications caused by external radiation. The prognosis for elderly patients with TM is much graver than for younger ones, and the treatment must be more aggressive, emphasizing the need for early diagnosis with prompt investigation and treatment. (9 Refs)

31. MEDULLARY CARCINOMA OF THE THYROID. DIAGNOSTIC AND THERAPEUTIC PROBLEMS.

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Recenti Prog Med; 71(3):274-305 1981

Of 700 patients with malignant thyroid cancer observed between 1960 and 1980, 28 (10 men, 18 women; 22-69 yr old) had medullary carcinoma of the thyroid (MCT). Among these MCT patients were four brothers and one sister. The mother had no pathology of the thyroid; the father was dead but, based on radiographic examination had been diagnosed to have had bilateral nodular hyperplasia of the thyroid, with multiple bilateral calcification. One brother had a suprarenal pheochromocytoma (SP) that was removed before resection of the thyroid. The other three had nephrolithiasis; all five siblings had multiple bilateral foci of the MCT. Another patient with the bilateral MCT had thyroidectomy, followed by uncon trollable hypertensive crisis and death 2 days later; at autopsy, two large SP were found. Fourteen patients with monolateral MCT and, when possible their relatives, were examined and had determinations for calcitonin (CT) and carcinoembryonic antigen (CEA), but no familial pathology was noted. Metastases (ME) of lymph nodes were observed in the 15 patients. Cycles of radiotherapy were administered to 22 patients, 10 of whom also received I131. Antiblastic therapy was not used. Of seven patients with multiple endocrine cancers, one died due to bilateral SP 2 days after surgery, one had the ME, the others were well, but four had elevated values of CT and CEA. Of the remaining 21 patients, 17 were living, 11 of whom were without signs of relapse or ME. Problems associated with diagnosis and therapy were discussed. (121 Refs) (In ITA)

32. THYROID HYPOFUNCTION AFTER EXPOSURE TO FALLOUT FROM A HYDROGEN BOMB EXPLOSION.

Larsen PR, Conard RA, Knudsen KD, Robbins J, Wolff J, Rall JE, Nicoloff JT, Dobyns BM

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JAMA; 247(11):1571-1575 1982

Thyroid function was evaluated in the Marshallese who were accidentally exposed to fallout-containing radioiodine isotopes in 1954. Measurements of thyrotrophin (TSH, thyroid-stimulating hormone) levels and free thyroxine (T4) index (FT4I) have revealed that, among 86 persons exposed on Rongelap and Allingnae atolls, 14 have shown evidence of thyroid hypofunction. This was first noted in some individuals about 10 years after exposure. Only two of these showed clinical evidence of hypothyroidism. The most marked TSH elevations were noted in nine persons exposed when younger than 6 years, with estimated doses to the thyroid from 390 to 2,100 rad. Most of this group subsequently had surgery for removal of thyroid nodules. The remaining five cases have been noted more recently among 36 surviving adults exposed at an older age who showed no other detectable thyroid abnormalities. This group had received estimated thyroid doses ranging from 135 to 335 rad and showed modest elevation of serum TSH levels (6 to 9 uU/mL) and a slightly subnormal FT4I. No abnormalities were found in persons on Utirik who received substantially less radiation, and hypothyroidism was present in less than 1% of the control, unexposed Marshallese. The high prevalence of a thyroid hypofunction in these persons indicates that this condition, as well as thyroid nodularity, can be a delayed complication of exposure to early fallout from a nuclear explosion. The fact that a significant fraction of the radiation to the thyroid was from short-lived radioiodine isotopes (132I, 133I, 136I), as opposed to 131I, may account for the severity of the thyroid damage. (Author abstract) (20 Refs)

33. MANAGEMENT OF HYPER AND HYPO THYROID CONDITIONS.

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Postgrad Med; 71(3):118-125,128-129 1982

Management of hyperthyroidism and hypothyroidism depends in large part on the cause and severity of the disease. In hyperthyroidism, a variety of etiologic, pharmacologic, and ablative approaches have been developed, each best suited to specific causes of thyroid excess. In hypothyroidism thyroid deficit must be identified as primary, secondary, or tertiary before hormone replacement therapy is initiated. In this article, attention centers on hyperthyroidism because of the more complex nature of this condition and its therapy. Hypothyroidism, including myxedema coma, is briefly considered. (Author abstract) (16 Refs)

34. ABNORMAL PLASMA HORMONE LEVELS IN WOMEN WITH BREAST CANCER.

Zumoff B, Korenman SG
Clinical Res. Center, Montefiore Hosp. and Medical Center, Inst. for Steroid Res., Bronx, NY, 10467
Banbury Rep; 8:143-168 1981

The 24-hr mean plasma concentrations of 14 hormones or hormone metabolites were measured in breast cancer patients, patients with cancer other than breast cancer, and women with noncancerous illnesses. Normal values of triiodothyronine and elevated levels of thyroxine were found in breast cancer patients. Adrenal androgens were decreased in women with premenopausal breast cancer. Plasma levels of luteinizing hormone were normal in most patients, and subnormal in some; 24-hr profiles were abnormal in all of seven luteal phase cancer patients studied. The significance of these results is discussed. (75 Refs)

35. BIOLOGIC MARKERS IN LUNG CANCER.

Vincent RG
Dept. Thoracic Surgery and Oncology, Roswell Park Memorial Inst., 666 Elm St, Buffalo, NY, 14263
Semin Respir Med; 3(3):184-193 1982

Specific biologic markers in lung cancer may be more commonly related to one histologic type of lung cancer than another. Such markers are classified as hormones, antigens, enzymes or proteins. The presence of tumor markers might permit screening for early malignant lesions,monitoring of the clinical course of previously diagnosed and treated tumors, or establishment of a selective differential diagnosis. Hormonal tumor markers include calcitonin, ACTH, lipotropin, parathyroid hormone, antidiuretic hormone, growth hormone, human chorionic gonadotropin, placental lactogen, melanocyte-stimulating hormone, prolactin, and 5-hydroxytryptophan. Proteins, antigens and antibodies that have been identified as possible tumor markers include ceruloplasmin, ferritin, tissue polypeptide antigen, Tennessee antigen, alpha 1-antitrypsin, carcinoembryonic antigen, pancreatic oncofetal antigen, beta 2-microglobulin, immunoglobulins, and alpha fetoprotein. Enzymes that may be useful as tumor markers include 5'-nucleotide phosphodiesterase isozyme-V, galactosyl-transferase II, amylase, creatine kinase, sialyltransferase, and placental alkaline phosphatase. Some of the nonspecific markers individually or in combination may be useful in the future in diagnosis, staging and therapy of lung cancer. (136 Refs)

36. PARANEOPLASTIC SYNDROMES IN LUNG CANCER.

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Semin Respir Med; 3(3):200-209 1982

Paraneoplastic syndromes are reviewed with particular emphasis on their relationship to lung cancer. Paraendocrine syndromes are those associated with ectopic hormone production, and usually occur in patients with lung cancer, although they have been reported in patients with other types of cancers. Approx 10% of lung cancer patients have paraendocrine syndromes. Differentiation of these syndromes may be difficult. Clinical characteristics of the syndromes associated with abnormal production of the following hormones are presented: ACTH, melanocyte-stimulating hormone, antidiuretic hormone-oxytocin-human neurophysin, parathyroid hormone-prostaglandin-nonmetastatic hypercalcemia, calcitonin hypercalcemia, calcitonin, human growth hormone and hypertrophic osteoarthropathy, human chorionic gonadotropin-follicular-stimulating hormone-human placental lactogen-production gynecomastia, prolactin, serotonin, insulin and glucagon, gastric and gut hormones, renin, multiple hormone production, and certain enzymes. Non-paraendocrine syndromes are those related to non-ectopic hormone production and may involve neuromuscular disorders, dermatologic disorders, hematologic disorders, and others. Recognition of these syndromes may lead to proper management and to a search for the underlying unrecognized malignancy. (74 Refs)

37. CARCINOMA OF THE LUNG WITH MARKED HYPERAMYLASEMIA AND ELEVATED SERUM CALCITONIN.

Roberts I, Chopra S, Warshaw AL
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Am J Gastroenterol; 77(1):43-44 1982

Ectopic production of multiple peptide hormones is a frequent concomitant of neoplasia. An elderly man with metastatic small cell carcinoma of the lung presented with back pain, a right hilar mass, and was demonstrated to have markedly elevated serum calcitonin and amylase levels. Polyacrylamide gel electrophoresis revealed a striking elevation of a 'salivary type' isoamylase. We report this case as an unusual association of production of both a peptide hormone and a nonhormonal peptide in a patient with a tumor of 'neural crest' origin. (Author abstract) (15 Refs)

38. THE DIFFERENTIAL DIAGNOSIS OF HYPERCALCEMIA: AN ALGORITHM FOR MORE EFFECTIVE USE OF LABORATORY TESTS.

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JAMA; 247(1):75-80 1982

An algorithm is presented to provide a cost-effective means of identifying the cause of hypercalcemia (myeloma or sarcoidosis, bone metastases, endocrine disorders, occult malignancy, or primary hyperparathyroidism). The procedure begins with a repeat serum calcium assay; if the repeat assay is normal, no further tests are performed, and if the assay shows continuing hypercalcemia, serum protein electrophoresis is performed. Other diagnostic procedures include: searching for bone metastases (if there is a present or past history of carcinoma), evaluation for myeloma or sarcoidosis, evaluation of endocrine disorders using appropriate laboratory tests, and withdrawal of any drugs that may have caused hypercalcemia. Assays for serum chloride, serum phosphorus, and alkaline phosphatase are performed if hypercalcemia has persisted for greater than 1 yr. If hypercalcemia had persisted for less than 1 yr and the searches for bone metastases, drug-induced hypercalcemia, myeloma, sarcoidosis, and endocrine disorders give negative results, the same laboratory tests and assays of parathyroid hormone, Hb, and hematocrit are performed, followed by a workup for occult malignancy if indicated. If the diagnosis is 'probable primary hyperparathyroidism', further tests and follow-up may be required to establish a diagnosis. (23 Refs)

39. RAPID RADIOIMMUNOASSAY FOR INSULIN AND ITS APPLICATION IN LOCALIZING OCCULT INSULINOMAS BY INTRAOPERATIVE PANCREATIC VEIN CATHETERIZATION.

Zick R, Hammer A, Otten G, Mitzkat HJ
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Eur J Nucl Med; 7(2):85-87 1982

Intraoperative pancreatic vein catheterization at laparotomy and immediate insulin determination of serum samples by rapid radioimmunoassay (RIA) allows localization of insulinomas during surgery and avoids risk of transhepatic catheterization. Two cases are described in which sonography, computed tomography, and selective arteriography did not yield clear diagnosis, but RIA of serum collected intraoperatively helped locate tumors. Serial sampling of tributaries to the vena mesenterica superior and vena lienalis showed locations of elevated insulin levels, which were confirmed by immediate resection of benign insulinomas in both cases. Removal of tumors were followed rapidly by reduced serum insulin levels. (10 Refs)

40. ON DIAGNOSTIC VALUE OF DETERMINATIONS OF CHORIONIC GONADOTROPIN AND TROPHOBLASTIC BETA1-GLYCOPROTEIN IN TROPHOBLASTIC DISEASE.

Grinevich IuA, Tatarinov IuS, Iugrinova LG, Olefirenko GA, Dotsenko IuS
Res. Inst. Roentgeno-Radiology and Oncology, Kiev, USSR
Vopr Onkol; 27(12):19-23 1981

The diagnostic value of determinations of the levels of chorionic gonadotropin (HCG) and trophoblastic beta1-glycoprotein (TBG) was studied in 160 cases of trophoblastic disease. Trophoblastic disease was diagnosed in 86% of cases, when HCG level was determined immunologically and in 100% - by radioimmunological means and in 86 and 33%, when TBG level was established by immunoradioautographical and immunodiffusion methods, respectively. The results of HCG and TBG assays by immunological and immunoradioautographical methods matches in 96% of cases. The said methods are highly specific and may find a wide application in diagnosing trophoblastic disease. The radioimmunological method of HCG assay is the most sensitive. However, in view of possible HCG synthesis in cases of other tumor, its application should be preferred in assessing the efficacy of therapy rather than for primary diagnosis of trophoblastic disease. (Author abstract) (8 Refs) (In RUS)

41. HYPERTENSION SECONDARY TO PHEOCHROMOCYTOMA.

Manger WM, Gifford RW
National Hypertension Association, Inc., 400 East 34th St., New York, NY, 10016
Bull NY Acad Med; 58(2):139-158 1982

Clinical expressions of pheochromocytoma (PCC), entities sometimes associated with PCC, differential diagnosis, diagnosis, and treatment are discussed. Most PCC secrete both norepinephrine (NEN) and epinephrine, but NEN usually predominates. Symptoms are due either to pharmacologic effect of excessive circulating catecholamines (CTA) or to complications of hypertension. Most commonly experienced are headache, generalized sweating, and palpitations. Clinical signs are hypertension, paroxysmal and sustained. Atypical manifestations are frequent when PCC occurs during childhood or pregnancy, or if the tumor arises in the urinary bladder. In the differential diagnosis of PCC, the disease entities may have to be considered. Indications for screening patients for PCC, laboratory and electrocardiographic findings, pharmacologic and biochemical tests, and preoperative location of PCC necessary for the diagnosis are presented. Preoperative treatment consists of excluding conditions that may increase excretion of CTA and their metabolites, and to determine in cases of familial PCC if medullary thyroid carcinoma or hyperparathyroidism is present. Propanolol should never be given to a patient with PCC without first creating alpha-adrenergic blockade because beta blockade may significantly elevate blood pressure. Postoperative hypotension has to be prevented by preoperative and intraoperative correction of blood volume deficits. Approx 75% of patients are normotensive following surgical removal, while the remainder have sustained hypertension without evidence of residual tumor. If a PCC has metastasized or cannot be totally resected, then as much tumor as possible has to be removed to reduce the functioning tissue to a minimum. (28 Refs)

EFFECTS ON NORMAL AND NEOPLASTIC CELLS AND TISSUES

42. ORGANIZATION OF PROVIRAL DNA AND PROTEIN COMPOSITION OF HORMONALLY STIMULATED C57BL/10 STRAIN-ASSOCIATED MOUSE MAMMARY TUMOR VIRUS.

Svec J, Matoska J, Keszeghova V, Hlavayova E
Cancer Res. Inst., Slovak Acad. Sciences, 812 32 Bratislava, Czechoslovakia
Neoplasma; 28(6):647-659 1981

Two continuous lines, BL-MaTU/A1 and BL-MaTU/S6, were established from C57Bl/10 mammary adenocarcinomas induced by DMBA-prolactin-estradiol treatment. Under in vivo stimulation with dexamethasone, insulin, prolactin, and prostaglandin A1, the cells produce detectable amounts of B-type particles with biochemical properties similar to the GR-MuMTV. Analysis of restriction endonuclease-generated fragments of cellular DNA revealed identical patterns in the integration sites and internal recognition sites of MuMTV proviral equivalents in the tumor cells and normal organs of C57Bl/10 strain mice. The restriction DNA fragments of C57Bl/10-associated MuMTV proviral DNA are closely related to those of the Balb/c-associated MuMTV. These results indicate the endogenous origin of MuMTV produced in the hormonally stimulated cultures of DMBA-prolactin-estradiol-induced C57Bl/10 mammary tumors. (Author abstract) (35 Refs)

43. PLASMA PROLACTIN ANALYSIS AS A POTENTIAL PREDICTOR OF MURINE MAMMARY TUMORIGENESIS.

Sinha YN, Siiteri, Dao TL, Meites J, Rosen JM, Korenman, Shiu, Sirbasku DA
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Banbury Rep; 8:377-394 1981

The correlation between plasma prolactin (PP) and breast cancer (BC) in humans, rats, and mice and possible reasons for the lack of correlation between PP and BC (metabolic clearance rate of prolactin (PR), conversion of PR into nonimmunodetectable forms, size heterogeneity of circulating PR, and immunologically unreactive form of PR in the pituitary) are discussed. A clinical correlation between PP and incidence of BC has not been found, possibly due to a lack of methods for quantification of all different molecular forms of PR present in the blood. (53 Refs)

44. PROLACTIN AND GROWTH HORMONE IN THE DEVELOPMENT, PROGRESSION, AND GROWTH OF MURINE MAMMARY TUMORS.

Welsch CW
Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:299-315 1981

The role of prolactin and growth hormone in the development and growth of spontaneous rodent mammary tumors, were examined. Growth of transplantable rodent mammary tumors, and development and growth of carcinogen-induced rat mammary tumors were also examined. Prolactin is important in initiating and promoting phases of murine mammary tumorigenesis, while the role of growth hormone appears to be less important. The role of growth hormone in the oncogenesis remains to be determined. (72 Refs)

45. PROSTATE CARCINOMA TUMOR SIZE IN RATS DECREASES AFTER ADMINISTRATION OF ANTAGONISTS OF LUTEINIZING HORMONE-RELEASING HORMONE.

Redding TW, Coy DH, Schally AV
Endocrine and Polypeptide Lab., Veterans Admin. Medical Center, New Orleans, LA, 70146
Proc Natl Acad Sci USA; 79(4,part1):1273-1276 1982

The effects of two potent antagonistic analogues of luteinizing hormone-releasing hormone (LH-RH) on the growth of two different models of rat prostate tumors have been investigated. Chronic administration of [NAc-p-F-DPhe1,p-Cl-DPhe2,DTrp3,6,D-Ala(10)]LH-RH (antagonist I) at 50 ug/day for 21 days significantly inhibited the growth of the chemical induced squamous cell carcinoma 11095 in Fischer 344 male rats. The weights of the pituitary, ventral prostate, and testes were not significantly altered. After 21 days of treatment with this analogue, serum luteinizing hormone (lutropin), follicle-stimulating hormone, and testosterone levels were markedly decreased. When male Copenhagen F-1 rats bearing the Dunning 3327H prostate adenocarcinoma were injected with antagonist I at 50 ug/day for 6 wk or with [NAc-p-Cl-DPhe1,2,DTrp3,DPhe6,DAla(10)]LH-RH (antagonist II) at 50 ug/day for 17 days, the percentage increase in tumor volume was decreased to half or less and the actual tumor volume was diminished 34-96% compared to controls. Tumor weight was decreased 30% and 89% after antagonist I and II, respectively, compared to untreated controls. The tumor doubling time was 3-to 4-fold longer in rats receiving the inhibitory analogues than in the controls. Treatment with antagonist II decreased the weight of the whole prostate, but neither antagonist changed the weight of testes, anterior pituitary gland, or adrenals. Serum luteinizing hormone, follicle-stimulating hormone, and testosterone levels in Copenhagen F-1 rats bearing Dunning tumors were significantly decreased after treatment with the inhibitory analogues, but progesterone levels were increased. The inhibitory effects of these antagonistic analogues on rat prostate tumors suggest that these compounds might be considered in the development of new types of therapy for prostate carcinoma and other endocrine-dependent neoplasias. (Author abstract) (32 Refs)

46. EVIDENCE THAT STIMULATION OF THYROTROPIN AND PROLACTIN SECRETION BY THYROTROPIN-RELEASING HORMONE OCCUR VIA DIFFERENT CALCIUM-MEDIATED MECHANISMS: STUDIES WITH VERAPAMIL.

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Endocrinology; 110(3):901-906 1982

TRH stimulation of TSH and PRL secretion requires Ca. We determined whether influx of extracellular Ca was involved in TRH action in TtT cells (mouse pituitary tumor cells in short term culture that produce TSH), in GH3 cells (clonal rat pituitary tumor cells that produce PRL), and in anterior pituitary cells in vitro derived from normal rats. TRH increased 45Ca uptake by TtT cells by 40% but had no effect on 45Ca uptake by GH3 cells. Verapamil, which totally inhibited 45Ca uptake by TtT and GH3 cells induced by depolarization with 50 mM K, was employed to block influx of extracellular Ca. Verapamil (50 uM) abolished the increment in 45Ca uptake by TtT cells caused by TRH. Verapamil had no effect on TRH-stimulated 45Ca efflux and PRL release from GH3 cells but partially inhibited TRH-stimulated 45Ca efflux and TSH release from TtT cells during perifusion. TRH-stimulated PRL release from GH3 cells was likewise not affected by verapamil during static incubation (7.2 -1.1 ng/ml vs 6.2 -1.2 ng), but TRH-stimulated TSH release from TtT cells was inhibited by 64% (from 5.5 -0.7 ngeq/ml to 2.0 -0.6 ngeq). Similar findings on the effects of verapamil on hormone release were obtained from nonneoplastic anterior pituitary cells; TRH-stimulated PRL release was not affected, but TRH-stimulated TSH release was inhibited by 50%. Hence, TRH did not cause Ca influx into mammotropic cells and TRH-stimulated PRL release was not affected when Ca influx was blocked by verapamil. In contrast, TRH appeared to cause Ca influx into thyrotropic cells, and TRH-stimulated TSH release was partially inhibited when Ca influx was blocked by verapamil. We suggest that TRH action in mammotrophs involves only mobilization of cellular Ca, whereas TRH action in thyrotrophs involves mobilization of cellular Ca and influx of extracellular Ca. (Author abstract) (29 Refs)

47. THE PHOSPHATIDYLINOSITOL CYCLE IN WRK-1 CELLS. EVIDENCE FOR A SEPARATE, HORMONE-SENSITIVE PHOSPHATIDYLINOSITOL POOL.

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Dept. Physiology and Biophysics, New York Univ. Medical Center, New York, NY, 10016
J Biol Chem; 257(5):2137-2139 1982

Using the vasopressin-sensitive rat mammary tumor cell line, WRK-1, we examined conditions under which vasopressin was able to stimulate turnover of prelabeled, radioactive phosphatidylinositol. Only cells which had been preincubated with 32Pi in the presence of hormone were able to subsequently respond to the hormone by increased loss of radioactivity from phosphatidylinositol. In addition, in experiments performed with uniformly labeled cells, we estimated that the hormone-sensitive phosphatidylinositol accounted for 17% of the total cellular phosphatidylinositol. Implications of these findings are discussed. (Author abstract) (11 Refs)

48. GROWTH INHIBITORY EFFECTS OF THYROID HORMONES ON ANDROGEN-DEPENDENT MAMMARY TUMOR CELLS.

Natoli C, Sica G, Natoli V, Scambia G, Iacobelli S
Laboratorio Endocrinologia Molecolare, Universita Cattolica del Sacro Cuore, Via della Pineta Sacchetti 644, 00168 Roma, Italy
J Steroid Biochem; 15:409-413 1981

Proliferative effects of thyroid hormones and their possible reaction with androgens were studied in Shionogi 115 mouse mammary carcinoma. Cells derived from this tumor are available in culture as androgen responsive (A cells) variant, whose growth is stimulated by physiological concentrations of androgens, and as the autonomuos variant (-A cells). Presence of triiodothyronine receptors in both A and -A cells was also investigated. Correspondence between binding capacity of the nuclear receptor and biological activity of various thyroid hormone analogues suggests that the proliferative effect is mediated via a receptor mechanism. (23 Refs)

49. EFFECT OF THYROID HORMONES ON ANDROGEN RESPONSIVENESS IN A MAMMARY TUMOR CELL LINE.

Sica G, Natoli C, Marchetti P, Iacobelli S
Istituto di Istologia ed Embriologia Generale, Universita Cattolica del Sacro Cuore, Largo Gemelli 8, 00168 Roma, Italy
J Steroid Biochem; 15:415-419 1981

Effects of thyroid hormones (TH) on androgen responsiveness (AR) were studied in Shionogi mouse mammary carcinoma cells (S115) and the variability of hormone response and duration of endocrine-induced remissions in human cancer regressions was investigated. Triiodothyronine (T3) at physiological concentrations slows down the loss of AR in S115 cells, cultured in the absence of testosterone. This is not mediated by the androgen receptor, since its level remains constant. T3 effect is more evident in the presence of AG1 x 10 anion-exchange resin which depletes serum of TH. (15 Refs)

50. HORMONAL REGULATION OF HUMAN BREAST CANCER CELLS IN VITRO.

Lippman M, Meites J, Welsch CW, Rosen JM, Segaloff A, Korenman SG, Nandi S, Sirbasku DA
Medical Breast Cancer Section, Medicine Branch, NCI, Bethesda, MD, 20205
Banbury Rep; 8:171-184 1981

Cultured breast cancer cell lines (most of which were derived from neoplastic effusions, often after treatment) differ from the original tumors in several important ways. Experiments with these cell lines must be designed and their results interpreted with great caution. Firm conclusions as to the absence of a given hormone response are particularly difficult to interpret. Positive results are much less ambiguous, but these can also give rise to misinterpretations. Nevertheless, the cell-culture approach provides several advantages in the investigation of hormonal interactions with human breast cancer. In particular, drug- and hormone-resistant variants of wild-type parental cell lines can be used to study the mechanisms of hormone dependence. Hormones now known to affect the growth or differentiated functions of human breast cancer cells (especially the MCF-7 cell line) include estrogens, glucocorticoids, androgens, thyroid hormones (the ZR-75-1 cell line is absolutely dependent on physiologic levels of triiodothyronine in the medium, and MCF-7 cells are also thyroid hormone dependent), and insulin. Vitamin A derivatives are required for normal epithelial differentiated and inhibit several types of chemical carcinogenesis in rats. Several human breast cancer cell lines contain separable binding activities for retinol and retinoic acid, but clinical trials of 13-cis-retinoic acid in breast cancer patients have not been encouraging. The roles of epidermal growth factor, vitamin D, progesterone, and prolactin in breast cancer growth are not yet clear. (46 Refs)

51. EXPERIMENTAL STUDY OF THE EFFECT OF VARIOUS DOSES OF CALCITONIN ON POSTRADIATION RECOVERY OF MAXILLA.

Nikitenko VA, Modiaev VP
Res. Inst. Medical Radiology, Obninsk, USSR
Med Radiol (Mosk); 26(12):38-43 1981

The effect of calcitonin (CT) on the postradiation recovery of the jaw bones was studied in Wistar rats. Animals were subjected to local irradiations of maxillofacial region (300 rads/day, 5x/wk, total dose 4,500 rads). Within 30 days after irradiations, animals received CT at 0.6, 2.5, 10, and 40 units/kg. Histological examination of maxilla specimens showed that CT at 0.6-2.5 units/kg enhanced osteogenesis. CT at 10-40 units/kg caused excessive formation of bone tissue. (12 Refs) (In RUS)

52. THE ACTIONS OF INSULIN AS A HORMONAL FACTOR IN BREAST CANCER.

Hilf R, Siiteri PK, Shellabarger, KorenmanSG, Rosen, Nandi
Dept. Biochemistry and Univ. Rochester Cancer Center, Univ. Rochester, Rochester, NY, 14642
Banbury Rep; 8:317-337 1981

Evidence implicating insulin as one of the hormones involved in the growth of breast cancer in animals (insulin-dependent and insulin-responsive tumors) is presented. Some of insuline actions related to neoplastic growth are described (insulin receptors and their regulation, insulin and glucose transport, insulin and amino acid transport, and insulin as a regulator of estrogen receptors). Clinical data and the role of insulin in human breast cancer are reviewed. Direct effects of insulin are stimulation and inhibition of tumor growth. Indirect effects are regulation of estrogen receptors and antagonism of insulin effects by estrogen. (73 Refs)

EFFECTS OF ENDOGENOUS AND EXOGENOUS AGENTS ON NON-STEROID HORMONE ACTIVITY

53. PROLACTIN-DEFICIENT VARIANTS OF GH3 RAT PITUITARY TUMOR CELLS: LINKED EXPRESSION OF PROLACTIN AND ANOTHER HORMONALLY RESPONSIVE PROTEIN IN GH3 CELLS.

Ivarie RD, Morris JA, Martial JA
Dept. Molecular and Population Genetics, Univ. Georgia, Athens, GA, 30602
Mol Cell Biol; 2(2):179-189 1982

Expression of prolactin (PL) and the hormonally responsive protein p21 was studied in variants of GH3 rat pituitary tumor cells. GH3 cells in vitro produced approx equal amounts of PL and growth hormone (GH). After exposure to ethylmethanesulfonate (EMS: 300 ug/ml) for 24 hr, survival of GH3 cells was 20-30%. Cultures of 3 of 12 surviving mutants (LP), produced PL in greatly reduced amounts (1.0-2.5% of the amount produced by wild-type GH3 cells). GH production by LP cells varied only approx twofold from GH production by wild-type cells. Radiolabeling experiments showed that reduced secretion of PL resulted from reduced synthesis of PL. Reduced synthesis of PL was repressible by dexamethasone. Reduction in PL synthesis was accompanied by a reduction in p21, which, like PL, is repressible by glucocorticoids (GC). Production of other GC-repressible proteins was not reduced in LP cells. PL production varied in different LP. In the B2 variant reversion to normal PL production occurred at a rate of approx 20%. In the B3 variant reversions occurred at a frequency of 0.5%. Reversion to normal PL production was accompanied by a return to normal amounts of p21, indicating that PL and p21 are closely linked. GH production was phenotypically stable in LP and in GH3 cells not exposed to EMS. Results suggest that EMS, an alkylating agent, promoted an epigenetic change in gene expression. (37 Refs)

54. RELATION OF NEUROLEPTIC DRUGS TO DEVELOPMENT AND GROWTH OF MAMMARY TUMORS.

Meites J, Aylsworth CF
Dept. Physiology, Neuroendocrine Res. Lab., Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:365-376 1981

Effects of neuroleptic drugs (ND) on secretion of anterior pituitary and target gland hormones, mechanisms by which ND influence anterior pituitary function, and effects of ND on development and growth of mammary tumors (MT) in murine species and in human subjects are reviewed. ND stimulate prolactin and inhibit gonadotropin secretion in animals and humans. Administration of ND can profoundly affect MT in rats and mice. A definite role for prolactin in MT development and growth has not been demonstrated, but estrogen has been shown to be of primary importance in humans. (71 Refs)

55. CHARACTERIZATION OF AN EARLY INHIBITORY EFFECT OF GLUCOCORTICOIDS ON STIMULATED ADRENOCORTICOTROPIN AND ENDORPHIN RELEASE FROM A CLONAL STRAIN OF MOUSE PITUITARY CELLS.

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Endocrinology; 110(3):892-900 1982

The ability of glucocorticoid steroid hormones to inhibit release of ACTH and endorphin has been studied in the mouse pituitary tumor cell strain, AtT-20/D16v. Inhibition of release of both peptides was first detectable at 30 min (to 80-90% of control release) and was maximal (30-50% of control) by 3-4 hr of pretreatment with dexamethasone (1 x 10(-6) M). Glucocorticoids did not consistently affect basal hormone release, but they inhibited release stimulated four- to eightfold by hypothalamic extract, phorbol esters, or 8-Br-cAMP but not high K-stimulated release. The inhibitory effect was glucocorticoid specific and dose dependent with ED50S for dexamethasone, corticosterone, and cortisol close to their reported Kds for binding to the cytoplasmic glucocorticoid receptor. Inhibition of release was blocked by cycloheximide (1 x 10(-5) M), suggesting that protein synthesis was required. Experiments were performed to determine the site of action of glucocorticoids. Steroid pretreatment for up to 6 hr had no effect on total intracellular content of ACTH or beta-endorphin, hormone biosynthesis, or intracellular and extracellular hormone degradation. These results show that the inhibitory action of steroids was not due to decreased hormone synthesis, as has been reported after longer periods (24-72 hr) of glucocorticoid treatment. Experiments with the tumor-promoting phorbol esters (used as model secretagogues) showed the pretreamtent of D16 cells with dexamethasone (1 x 10(-6) M) did not alter the binding of [3H]phorbol dibutyrate to its specific receptor on these cells, indicating that glucocorticoids do not act by interfering with binding of secretagogues to the cells. Furthermore, glucocorticoids did not affect the ED50 for stimulation of ACTH release by phorbol esters, but they reduced the magnitude of maximum response. We conclude that an early action of glucocorticoids on D16 cells is to inhibit the release of ACTH and beta-endorphin by a mechanism that is independent of the synthesis and degradation of the secretory peptides but which involves the synthesis of new protein. (Author abstract) (31 Refs)

56. SEROTONIN AND HISTAMINE PRODUCTION BY HUMAN CARCINOID CELLS IN CULTURE.

Debons-Guillemin MC, Launay JM, Roseto A, Peries J
(c/o Peries) Dept. d'Oncologie Experimentale, Unite 107 INSERM, L.O.I., Hopital Saint-Louis, 2 Place du Docteur Fournier, 75010 Paris, France
Cancer Res; 42(4):1513-1516 1982

We are reporting on the first human carcinoid cells ever cultured in vitro. These cells, termed CGP, originated from a jejunal carcinoid tumor. Before tumor resection, the 29-yr-old male patient presented high levels of blood serotonin and histamine and also of urinary serotonin and 5-hydroxyindole-acetic acid; values returned to normal 9 days after resection. CGP cells exhibit a very slow multiplication rate; generation time is about 10 days. From the first subculture, the main cytological, ultrastructural, and biochemical features of CGP cultures remain unchanged. The cells show most of the enterochromaffin cell histomorphological characteristics; for example, cytoplasmic granulations, specific of argyrophilic cells, can be seen both by electron microscopy and by light microscopy (preceded by silver impregnation). The high amounts of serotonin and histamine found by highly specific radioenzymatic assays in the supernatant of CGP cultures indicate that, after 6 mo (25 subcultures), CGP cells have retained the main metabolic characteristics of the original tumor, ie, the ability to synthesize, store, and release both serotonin and histamine. (Author abstract) (14 Refs)

57. HUMAN ROTAVIRUSES INCREASE SEROTONIN RELEASE FROM HUMAN INTESTINAL CARCINOID CELLS CULTURED IN VITRO.

Roseto A, Cavalieri F, Debons-Guillemin MC, Sitbon M, Launay JM, Peries J
Departement d'Oncologie Experimentale, U107 INSERM, L01 CNRS, Hopital Saint-Louis, 2, Place du Docteur-Fournier, 75010 Paris, France
Ann Virol; 132(3):383-388 1981

The ability of human rotaviruses purified from diarrheic stools of pediatric patients to increase serotonin release from intestinal wall cells was studied in virus-infected cells cultured from an intestinal carcinoid tumor. A seven-fold increase in serotonin levels was observed in supernatants of infected cultures harvested 12 hr post-infection. No increase in serotonin was demonstrable either before or after the 12-hr point. Increases in lactate dehydrogenase and histamine were observed at the 6-hr point. (18 Refs)

58. PRODUCTION OF IMMUNOREACTIVE CALCITONIN BY MYELOID LEUKAEMIA CELLS.

Foa R, Oscier DG, Hillyard CJ, Incarbone E, McIntyre I, Goldman JM
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Br J Haematol; 50(2):215-223 1982

Raised plasma levels of immunoreactive human calcitonin (i-HCT) have been found in patients with chronic granulocytic leukemia (CGL) in chronic phase and myeloblastic transformation and in patients with acute myeloid leukemia at presentation and in relapse. In CGL levels were significantly higher in myeloblastic transformation than in the chronic phase. Leukemia cells were cultured in a short-term liquid culture system in which little cell proliferation occurs and in a two layer blast-cell colony system which permits blast-cell proliferation. i-HCT was identified in supernatant media from cells cultured in both systems but levels were substantially higher in media collected from cells cultured in the latter system. These results suggest that i-HCT is synthesized by proliferating blast cells. (Author abstract) (7 Refs)

59. THE EFFECT OF ALTERED LUMINAL NUTRITION ON CELLULAR PROLIFERATION AND PLASMA CONCENTRATIONS OF ENTEROGLUCAGON AND GASTRIN AFTER SMALL BOWEL RESECTION IN THE RAT.

Sagor GR, Al-Mukhtar MY, Ghatei MA, Wright NA, Bloom SR
(c/o Bloom) Dept. Medicine, Royal Postgraduate Medical Sch., London, England
Br J Surg; 69(1):14-18 1982

Luminal nutrition is known to have a trophic effect on small bowel mucosa after intestinal resection. Humoral agents, however, may also contribute to this process. Two of the proposed humoral agents, enteroglucagon and gastrin, were therefore investigated after intestinal resection and transection in the rat, and changes in their concentration in the plasma were related to cellular proliferation. Forty-eight male Wistar rats had either 75% proximal small bowel resection or jejunal transection. The animals were further divided into three groups, each with a different nutritional intake. The first group were allowed food ad libitum. The second group were kept under hypothermic conditions which resulted in hyperphagia, while the last group were nourished intravenously. A further eight animals had a laparotomy only (sham operation). All animals were killed 12 days after operation, plasma enteroglucagon and gastrin were measured, while determination of the crypt cell production rate was used to denote cellular proliferation. In each group resected rats had significantly higher crypt cell production rates and greater enteroglucagon levels compared with transected animals. However, only in the normally fed group was plasma gastrin increased in resected animals, there being no significant difference in the plasma concentration of this peptide in transected compared with resected rats, in both the intravenously fed and hyperphagic groups. In the models studied enteroglucagon appears to be a more likely candidate for a humoral trophic agent than gastrin in intestinal adaptation. (Author abstract) (41 Refs)

60. CARBOHYDRATE METABOLISM AND ENDOCRINE FUNCTION IN THE PANCREAS REMNANT AFTER MAJOR PANCREATIC RESECTION.

Mizumoto R, Kawarada Y, Goshima H, Tamaki H, Sekoguichi T, Tomikawa I
First Dept. Surgery, Mie Univ., Sch. Medicine, Tsu, Mie 514, Japan
Am J Surg; 143(2):237-243 1982

Changes in glucose tolerance, in secretion of pancreatic hormones and in the islets of the pancreas were investigated after major resection of the pancreas in dogs to elucidate the pathophysiologic features of carbohydrate metabolism and the difference in the amount of insulin required in diabetes after total and partial pancreatectomy. In diabetes after 90% or more pancreatectomy, both insulin secretion and the function of the anti-insulin system decreased, associated with degeneration of the islet B, A, and D cells. The required insulin amount was similar to that needed after total pancreatectomy. Diabetes developed more than 6 wk after 70 to 90% pancreatectomy, and insulin secretion decreased but the function of the anti-insulin system was accentuated with an increase in plasma glucagon levels, associated with degeneration in B cells but not in A and D cells. The amount of insulin required was 3 to 4x greater than that needed after total pancreatectomy. (Author abstract) (15 Refs)

61. REVERSAL OF DIABETES BY THE ISOTRANSPLANTATION OF NICOTINAMIDE-STREPTOZOTOCIN-INDUCED ISLET ADENOMA IN RATS.

Dixit PK, Bauer GE, Younoszai R, Hegre O
Dept. Anatomy, Medical, Sch., Univ. Minnesota, 4-141 Jackson Hall, 321 Church St., S.E., Minneapolis, MN, 55455
Transplantation; 33(2):163-167 1982

The effect of syngeneic transplantation of islet tumors induced by streptozotocin-nicotinamide treatment into Fisher inbred diabetic rats was studied. Transplantation of 10 mg of tumor tissue under the kidney capsule of severely diabetic animals resulted in complete amelioration in 9 of 14 animals. Partial improvement was noted in three animals, whereas only one animal showed no change in diabetic condition within 4 mo. Improvement in diabetes was accompanied by gain in body wt, decrease in blood sugar level and urinary glucose excretion, and normalization of glucose tolerance. After removal of the kidney containing the tumor graft, the animals reverted to a severe diabetic condition, suggesting that the tumor graft supplied the insulin needs of the diabetic animal. The graft tissue exhibited in vitro insulin synthesis and secretion in response to 16.7 mM glucose. (Author abstract) (16 Refs)

RECEPTOR/ BINDING SITES

62. PROLACTIN, PITUITARY HORMONES, AND BREAST CANCER.

Shiu RP, Lippman M, Rosen JM, Sirbasku DA, Welsch CW
Dept. Physiology, Faculty Medicine, Univ. Manitoba, Winnipeg, Manitoba R3E OW3, Canada
Banbury Rep; 8:185-196 1981

The number of prolactin receptors (PR) in 11 human breast cancer cell lines ranged from 25,800 to 1,094; there were 1,700 in a normal cell line. The biological significance of PR and biological responses produced by PR are discussed. No growth-regulatory effect of prolactin has been demonstrated. In vivo, human breast cancer cells were responsive to estrogen and pituitary hormones. (25 Refs)

63. EVIDENCE FOR AN ACTIVE STEP IN THYROID HORMONE TRANSPORT TO NUCLEI: DRUG INHIBITION OF L-125I-TRIIODOTHYRONINE BINDING TO NUCLEAR RECEPTORS IN RAT PITUITARY TUMOR CELLS.

Halpern J, Hinkle PM
Dept. Pharmacology, Cancer Center, Univ. Rochester Sch. Medicine, Rochester, NY, 14642
Endocrinology; 110(3):1070-1072 1982

When added to intact GH4C1 or GH3 cells, cytochalasin b, dansylcadaverine, and chloroquine inhibited the binding of L-125I-triiodothyronine (T3) to nuclear receptors within 30 min. These drugs also reduced the amount of 125I-T3 in the post-nuclear supernatant fraction of cells lysed with Triton X-100. If 125I-T3 was added before the drugs, 125I-T3 that was already bound did not dissociate, but further binding was blocked. Inhibition due to 10 uM cytochalasin b or 150 uM dansylcadaverine was reversible within 2 hr of drug removal, and inhibition due to 150 uM chloroquine was partially reversible. Drug inhibition was overcome as the T3 concentration was raised. These drugs did not significantly inhibit 125I-T3 bind ing to isolated nuclei, and nuclei isolated from drug-treated cultures bound as much 125I-T3 as control nuclei. The results suggest that thyroid hormones reach their nuclear binding sites by an active transport process which is inhibited by the drugs studied. (Author abstract) (10 Refs)

64. PRESENCE OF 1,25-DIHYDROXYVITAMIN D3 RECEPTORS IN ESTABLISHED HUMAN CANCER CELL LINES IN CULTURE.

Frampton RJ, Suva LJ, Eisman JA, Findlay DM, Moore GE, Moseley JM, Martin TJ
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Cancer Res; 42(3):1116-1119 1982

Receptors for 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] have been described in several human breast cancer cell lines and more recently in human melanoma. The presence of 1,25-(OH)2D3 receptor (1,25-DR) in two cultured breast cancer cell lines was associated with receptors for calcitonin, another hormone thought to have effects on calcium handling. Therefore, it seemed important to examine a range of established human cancer cell lines for the presence of receptors for 1,25-(OH)2D3 and calcitonin. Thirty-three cancer cell lines were examined. 1,25-DR was found to be present in 23 lines, while calcitonin receptors were not detected in any of them. the 1,25-DR from several cell lines sedimented at about 3.5S in sucrose density gradients, had the appropriate specificity for vitamin D metabolites, had Kds of 0.8 x 2.2 x 10(-11) M, and had receptor concentrations of 12 to 99 fmol/mg protein. Ten malignant melanoma and 9 colonic carcinoma lines constituted the largest groups of carcinoma cell lines, and 7 and 8, respectively, of these were 1,25-DR positive. The high frequency of 1,25-DR positivity in the cultured colonic carcinoma cells is quite different from the low frequency of 1,25-DR in primary colonic carcinomas. It was also interesting that both of two cell lines derived from patients who had had both bone metastases and malignant hypercalcemia were 1,25-DR positive. These various cell lines may provide useful models for the examination of 1,25-(OH)2D3 action in vitro. (Author abstract) (31 Refs)

65. SPECIFIC HIGH AFFINITY BINDING SITES FOR SOMATOSTATIN-28 ON PANCREATIC BETA-CELLS: DIFFERENCES WITH BRAIN SOMATOSTATIN RECEPTORS.

Reubi JC, Rivier J, Perrin M, Brown M, Vale W
Peptide Biology Lab., Salk Inst., P.O. Box 85800, San Diego, CA, 92138
Endocrinology; 110(3):1049-1051 1982

Saturable and high affinity binding sites have been obtained for an iodinated somatostatin-28 (SS-28) analog, [Leu8,D-Trp22,125I-Tyr25] SS-28, in a membrane preparation from hamster insulinoma, mainly composed of pancreatic beta-cells. Specific binding is maximal after 1 hr incubation at 22 C and represents 65% of the total binding. KD for [Leu8,D-Trp22,Tyr25] SS-28 is 0.25 nM with the number of s ites corresponding to 68 fmol/mg protein. The Kd for SS-28 (1 nM) is more than 5 times lower than that for SS-14. SS-28 analogs, such as [D-Trp22] SS-28 and analogs which selectively inhibit insulin release in vivo (Des-Asn5[D-Trp8,D-Ser13] SS-14 and Des-Asn19[D-Trp22,D-Ser27] SS-28), are the most potent compounds in this assay. C-terminal replacement of L-cysteine by D-cysteine reduces the apparent affinity of SS analogs. Unrelated peptides and the inactive analog Des-Trp8-SS-14 have no affinity for insulinoma binding sites. There are differences between the insulinoma SS binding sites and those monitored under similar conditions from rat cerebral cortex. In cerebral cortex, SS-14 and SS-28 have similar affinity for the binding sites, and the insulin selective analogs are less potent than SS-14. It is concluded that pancreatic beta-cells, as well as brain, possess high affinity binding sites for SS, but that they differ in some of their pharmacological properties. (Author abstract) (16 Refs)

66. INSULIN RECEPTORS IN HUMAN CANCER.

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Br J Cancer; 44(6):917-920 1981

A variety of human cancers were tested for specific receptors for insulin. Sixty-seven tissue samples (40 tumors, 24 fat, 3 muscle) were obtained during surgery were homogenized; the pellet contained receptors for prolactin and insulin. The insulin-binding assay was performed using porcine unlabeled and insulin labeled with 125I using chloramine-T. Specific binding was measured using Scatchard analysis. All specific binding values were adjusted to a membrane-protein concentration of 3.0 mg/ml; range of values found was 0.5-5.0 mg/ml. Significant insulin binding was detected in all tumor specimens except one breast-tumor sample which had a low yield of membrane protein of 1.5 mg/ml compared to an av value of 33.1 mg/ml. 125I-insulin binding to different types of tumor was compared with insulin binding to normal placenta, fat and muscle. Degradation of 125I-insulin by membranes from normal and tumor tissue was compared in one specimen of colon carcinoma. Little difference was detected in the rate of insulin degradation. Rate of degradation of labeled insulin also appeared similar in different types of tumor (colon, stomach, and breast). Affinity of binding decreased with increasing receptor occupancy. Apparently insulin receptors in normal cells are preserved during malignant transformation. However, other studies have shown that tumors can also synthesize ectopic hormone receptors. Results suggest that insulin binding is a common property of human cancer, and that insulin may help maintain or stimulate the growth of human tumors. (13 Refs)

OTHER RELATED STUDIES

67. RECENT ADVANCES IN THE CONTROL AND FUNCTION OF THE ANTERIOR PITUITARY.

Stonesifer LD, Kohler PO
Dept. Medicine, Univ. Arkansas Medical Sciences, 4301 W. Markham, Little Rock, AR, 72205
Clin Biochem; 14(5):237-242 1981

Major advances in our understanding of the synthesis and release of anterior pituitary hormones have been made over the past several yr. Neurons of the hypothalamus have been found to serve as 'neuroendocrine transducers' in that they have both electrical and secretory functions. Peptidergic neurons respond to appropriate stimuli with a release of hypothalamic factors into the hypophyseal-portal system. These factors or hormones ultimately control the endocrine function of anterior pituitary cells. Three hormones, thyrotropin releasing hormone, gonadotropin releasing hormone, and somatostatin, have been identified, synthesized and tested for clinical applications. The clinical assessment of pituitary function has been greatly improved by new and improved radioimmunoassays. One of the recent clinical advances in the area of pituitary disease has been the determination of the relatively high frequency of prolactinomas. Prolactin secreting microadenomas are an important and treatable cause of amenorrhea and infertility in young women. In addition, many pituitary tumors previously believed to be nonfunctional or 'chromophobe adenomas' appear to be prolactinomas. Many new diagnostic and therapeutic techniques are continuing to be developed to improve our management of patients with hypothalamic-pituitary disease. (Author abstract) (70 Refs)

68. HORMONES AND BREAST CANCER.

Pike MC, Siiteri PK, Welsch CW
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep 8: 491 pp., 1981.

Sessions held to discuss the relationship between hormones and breast cancer (BC) consisted of the following topics: review of BC epidemiology (as it relates to menarche, pregnancy, and menopause, body size and BC risk), endocrinology of women at risk of BC (hormone profiles in young women at risk of BC with analysis of ovarian function during theelarche, menarche, and menopause, and after childbirth, endocrine maturation during female puberty, reproductive endocrinology and BC in women, increased availability of serum estrogens in BC), review of studies attempting to establish endogenous hormones as important in human BC (estrogens, progesterone, and prolactin in human BC, prospective study of relation between thyroid function and BC, and abnormal plasma hormone levels in women with BC), in vitro studies of human breast tissue (hormonal regulation of human BC cells in vitro, prolactin, pituitary hormones, and BC, estrogen receptor assays in familial and nonfamilial BC), exogenous hormones and BC (epidemiological studies of the role of exogenous estrogens in BC etiology and hormone therapy), other exogenous factors and BC (e pidemiological studies of mutagenicity of breast fluids and BC risk, diet and hormone metabolism in BC), hormones and genesis of progression of murine mammary tumors (ovarian steroid hormones, prolactin, growth hormone, insulin, pituitary and steroid hormones, pregnancy and lactation, neuroleptic drugs, and plasma prolactin analysis), and mechanism of hormone action (regulation of casein gene expression in hormone-dependent mammary cancer, control of estrogen-responsive tumor growth, and role of hormones in mammogenesis and carcinogenesis). (453 Refs)

69. RECENT ADVANCES IN PARATHYROID HORMONE RESEARCH.

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Lab. Molecular Endocrinology, Massachusetts General Hosp., Harvard Medical Sch., Boston, MA, 02114
Clin Biochem; 14(5):223-229 1981

The introduction of blood calcium determinations as part of routine health screening procedures in this country has led to the discovery of a much higher incidence of primary hyperparathyroidism than was recognized previously. Research efforts have focused on studies of the cellular defects in the regulation of parathyroid hormone biosynthesis and secretion that are characteristically found in adenomatous and hyperplastic parathyroid glands. The available evidence indicates that the secretory defect probably resides at two levels; (1) a defect in the calcium sensor of the abnormal glands ('set-point' error) and (2) an exaggeration of a small component of autonomous hormone secretion that becomes relevant due to the large mass of glandular tissue. Regulation of parathyroid hormone synthesis appears to be at the level of cell replication (hyperplasia) and at the level of intracellular turnover of hormone. Marked heterogeneity of hormone in the circulation arises as a result of both glandular and extraglandular cleavages of hormone and the predominant circulating form of the hormone are biologically inactive, COOH-terminal fragments. Because most cases of hypercalcemia that accompany cancer are caused by humoral substances other than parathyroid hormone, sensitive radioimmunoassays that detect COOH-terminal fragments should distinguish patients with hypercalcemia due to cancer from those with primary hyperparathyroidism. (Author abstract) (35 Refs)

70. CALCIUM REGULATION.

Raisz LG

Div. Endocrinology and Metabolism, Dept. Medicine, Univ. Connecticut Health Center, Farmington, CT, 06032

Clin Biochem; 14(5):209-212 1981

Normal calcium regulation depends on the complex interactions of several systems. The specific calcium regulating hormones, parathyroid hormone, calcitriol and calcitonin, affect calcium and phosphorus concentration and supply by acting on bone, kidney and intestine. The changing concentration and supply of ions not only regulate these hormones, but may also influence the function of the target organs, particularly bone, directly. Systemic hormones such as growth hormone and somatomedins, glucocorticoids, sex hormones and thyroid hormone are essential for skeletal growth and development and interact with calcium regulators. Prostaglandins and osteoclast activating factor may be important in local regulation of bone. Disorders of calcium regulation are common, particularly hypercalcemia; however, measurements of parathyroid hormone are not yet ideal and the factors which produce hypercalcemia in malignancy have not been identified. The role of calcium regulating hormones in the pathogenesis and treatment of osteoporosis is controversial. Solution to these problems may be dependent on the identification of additional factors which influence mineral metabolism. (Author abstract) (30 Refs)

71. IMMUNOMODULATION WITH THYMIC HORMONES IN NEOPLASTIC DISORDERS.

Patt YZ
Dept. Developmental Therapeutics, Univ. Texas M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer Bull; 33(6):265-271 1981

The interaction between thymic hormones and T-cell subsets in neoplastic disorders is discussed. Topics include the endocrine role of the thymus gland, thymosin fraction V, biologic studies with thymosin, thymic humoral factor, facteur thymique serique, thymopoietin II, and the role of thymic hormones in treatment of cancer. Studies with crude thymic extracts should be replaced by studies with well-characterized thymic peptides in well-defined groups of cancer patients. (67 Refs)

72. TUMORS OF THE ENDOCRINE PANCREAS.

Friesen SR
Dept. Surgery, Univ. Kansas Medical Center, Kansas City, KS, 66103
N Engl J Med; 306(10):580-590 1982

Pancreatic endocrinopathies are discussed with respect to the formulation of the amine-precursor uptake and decarboxylation (APUD) concept, the study of evolution of pathogenetic types of APUD-cell dysplasias, advances in diagnosis and tumor localization, new therapeutic methods, and the clinical recognition of syndromes. Ectopic pancreatic endocrine tumors described include glucagonoma (diabetes-dermatitis syndrome), pancreatic polypeptide islet-cell tumor, and carcinoid tumor of the pancreas (atypical carcinoid syndrome). Ectopic endocrine tumors of the pancreas include pancreatic gastrinoma (ectopic ulcerogenic syndrome), vipoma of the pancreas (watery-diarrhea syndrome), pancreatic corticotropinoma (ectopic-ACTH syndrome), and others. Diagnosis of these pancreatic tumors has been improved with recent developments in the quantitative measurement of circulating polypeptide hormones and in the cytochemical identification of APUD-cell tumors. (108 Refs)

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HORMONES IN CANCER-RELATED BIOLOGY

Non-Steroid Hormones

SERIES CB24 No. 82/08
AUGUST, 1982

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CHARACTERIZATION OF NON-STEROID

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

HORMONES IN EXPERIMENTAL AND IN VITRO SYSTEMS

1. INTRODUCTION OF RAT GROWTH HORMONE GENE INTO MOUSE FIBROBLASTS VIA A RETROVIRAL DNA VECTOR: EXPRESSION AND REGULATION.

Doehmer J, Barinaga M, Vale W, Rosenfeld MG, Verma IM, Evans RM
The Salk Inst., San Diego, CA, 92138
Proc Natl Acad Sci USA; 79(7):2268-2272 1982

We have introduced the rat growth hormone gene into mouse fibroblasts via a retroviral DNA vector. The ability of the viral DNA to induce foci in the recipient cells was used as a dominant selection marker. Several copies of rat growth hormone DNA were integrated in the mouse cells. The transformed mouse cells expressed rat growth hormone-specific mRNA and secreted mature rat growth hormone. In rat cells, the expression of this gene is regulated by glucocorticoids. We demonstrate that hormone-dependent regulation transfers with the clone and thus appears to be an intrinsic property of the gene or its RNA products. (Author abstract) (27 Refs)

2. [HALF-CYS4,HALF-CYS(10)]-ALPHA-MELANOCYTE-STIMULATING HORMONE: A CYCLIC ALPHA-MELANOTROPIN EXHIBITING SUPERAGONIST BIOLOGICAL ACTIVITY.

Sawyer TK, Hruby VJ, Darman PS, Hadley ME
Dept. Chemistry, Univ. Arizona, Tucson, AZ, 85721
Proc Natl Acad Sci USA; 79(6,part1):1751-1755 1982

Alpha-Melanocyte-stimulating hormone (alpha-melanotropin; alpha-MSH) is a linear tridecapeptide (Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val NH2) that reversibly darkens amphibian skins by stimulating melanosome (pigment granule) dispersion within melanophores. By using a number of in vitro melanocyte assays, we have examined the conformational requirements for alpha-MSH activity. Synthesis of [half-Cys4,half-Cys(10)]-alpha-MSH, a cyclic, conformationally restricted 'isoteric' analogue of alpha-MSH, provided a melanotropin with a potency greater than 10,000x that of the native hormone in stimulating frog (Rana pipiens) skin darkening. The cyclic analogue also showed substantially prolonged activity relative to the native hormone. [half-Cys4,half-Cys(10)]-alpha-MSH was approx 30x more potent than alpha-MSH in stimulating lizard (Anolis carolinensis) skin melanophores in vitro. By using a cell-free Cloudman S-91 mouse melanoma plasma membrane preparation, we found the cyclic analogue to be approx 3x as potent as the native hormone in stimulating adenylate cyclase activity. These results provide insight into the conformational requirements for biological activity of alpha-MSH, and the comparative conformational requirements of alpha-MSH at a number of pigment cell receptors. (Author abstract) (28 Refs)

3. ENHANCEMENT OF HUMAN B LYMPHOCYTE DIFFERENTIATION IN VITRO BY THYROID HORMONE.

Paavonen T
Transplantation Lab., Univ. Helsinki, Haartmaninkatu 3 A, SF 00290 Helsinki 29, Finland
Scand J Immunol; 15(2):211-215 1982

A study was made of the regulatory influence of a thyroid hormone, triiodothyronine (T3), on human blood T- and B-lymphocyte responses in vitro. Blood lymphocytes were stimulated with the T-cell mitogens concanavalin A (Con A) and phytohemagglutinin (PHA), with the T-dependent B-cell activator pokeweed mitogen (PWM), and with the T-independent B-cell activator Staphylococcus aureus Cowan I bacteria in the presence of various hormone concentrations. T3 did not stimulate T-cell proliferation. The number of immunoglobulin-containing and -secreting cells (plasmablasts) was increased in PWM and Staph aureus cultures treated with T3. The maximal enhancement was reached at a concentration of 10(-9) -10(-7) M T3. Cell fractionation techniques revealed that T3 apparently had a direct stimulatory effect on B-cell differentiation. (Author abstract) (18 Refs)

4. HUMAN LUNG SMALL-CELL CARCINOMA CONTAINS BOMBESIN.

Erisman MD, Linnoila RI, Hernandez O, DiAugustine RP, Lazarus LH
(c/o Lazarus) Lab. Pulmonary Function and Toxicology, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
Proc Natl Acad Sci USA; 79(7):2379-2383 1982

The presence of immunoreactive bombesin in a human lung small-cell carcinoma grown in nude mice was established by several criteria: (i) Radioimmunoassay of tissue extracts for bombesin revealed approximately 6.5 pmol/g of tissue; (ii) bombesin was found in 12-14% of the tumor cells by immunohistochemical localization; (iii) gel filtration of small-cell carcinoma extract on Sephadex G-75 and Bio-Gel P-4 gave only a single peak of immunoreactivity, which occurred at the elution vol of bombesin; and (iv) reverse-phase HPLC of acid-solubilized extracts separated the immunoreactive material into three discrete peaks, one of which eluted with a retention time identical to that of synthetic bombesin. The presence of bombesin may represent the ectopic expression of this peptide in small-cell carcinoma, because immunoreactive bombesin was found in human fetal and neonatal lung but apparently not in adult lung tissue. The immunoreactive bombesin previously found in mammalian tissues is considerably larger than amphibian bombesin; these data substantiate the presence of a mammalian form of bombesin in a human tumor that may have a structure similar to that of the amphibian peptide. (Author abstract) (52 Refs)

5. SOME THOUGHTS OF THE NATURE OF ERYTHROPOIETIN-RESPONSIVE CELLS.

Goldwasser E
Dept. Biochemistry, Univ. Chicago, Chicago, IL, 60637
J Cell Physiol; Suppl1:133-135 1982

Effects of addition of erythropoietin (EPO) on pluripotent hemopoietic stem cells (CFU-S) were studied using cells grown in liquid culture. Results did not agree with the established opinion that CFU-S were unaffected by EPO, since both an increase due to EPO in erythroid spleen colonies and a decrease in nonerythroid spleen colonies due to EPO was observed. The suggestion that EPO-responsive cells might include pluripotent hemopoietic stem cells does not fit with the unipotent, committed stem cells hypothesis. (8 Refs)

CLINICAL, DIAGNOSTIC AND PROGNOSTIC STUDIES

6. METERGOLINE IN THE MANAGEMENT OF HYPERPROLACTINEMIC AMENORRHEA AND ANOVULATION.

Falsetti L, Voltolini AM, Crosignani PG, Lotti G, Travaglini P, Faglia G, Cianci A, Palumbo G, Praga C, Pontiroli AE
(c/o Pontiroli) Cattedra di Clinica Medica 8, Ospedale S. Raffaele, I-20132 Milan, Italy
Gynecol Obstet Invest; 13(2):108-116 1982

Metergoline (MRG: 12 mg/day x 90) was given to 84 women with elevated serum prolactin (PRL) levels. The cause of hyperprolactinemia (HPL) was a pituitary adenoma in 18/84, neuroleptics or oral contraceptives in 7/84, postpartum HPL in 6/64, and unknown in 53/64. The major complaints were amenorrhea in 70/84 and anovulation in 14/84; galactorrhea was present in 50/84. The 90-day course of MRG was completed by 79 patients. Amenorrhea disappeared in 61/65 patients who completed the trial; 59/61 responded within the first 2 mo of treatment. The first menstrual period was followed by other periods in 58/61 patients. Galactorrhea disappeared in 40/50 patients. Ovulation returned in 13/14 evaluable anovulatory patients. All patients were advised to practice nonhormonal contraception, but 14 women became pregnant; 12/14 pregnancies proceeded uneventfully to normal delivery. Serum PRL levels were reduced in 76/79 patients who completed the planned course of MRG. Two of the failures were in patients with pituitary microadenomas, the third had idiopathic amenorrhea. In general, serum PRL levels were reduced to a greater extent in patients who obtained ovulatory cycles than in those who did not, however, some patients achieved ovulatory cycles although their serum PRL levels remained elevated. In 49 patients, the trial was continued for an additional 2 mo, with a reduced MRG dose (8 mg/day; 24/49) or placebo (25/49). Amenorrhea returned within 2 mo in 16/25 placebo-treated and only 5/24 MRG-treated patients. Serum PRL levels increased when amenorrhea recurred. It is concluded that MRG is a safe, effective agent for the treatment of HPL amenorrhea and anovulation. (20 Refs)

7. THERAPEUTIC EFFECT ON GALACTORRHEA AND STERILITY IN PROLACTIN-SECRETING PITUITARY ADENOMAS.

Sato O, Tanabe S, Tsuchita H, Nakagawa T, Inoue Y, Daibo M, Uede T, Hotta H
Dept. Neurosurgery, Sapporo Medical Coll., Sapporo 060, Japan
Neurol Med Chir (Tokyo); 21(11):1123-1133 1981

The authors investigated factors responsible for cessation of galactorrhea or restoration of ovulation in 30 women with PRL-secreting pituitary adenomas after surgery with or without bromocriptine. All the patients complained of sterility and 25 patients had galactorrhea. Microsurgical removal of adenomas was performed in all the patients and 15 patients received oral bromocriptine after surgery on account of sustained elevated serum PRL levels. Galactorrhea ceased in 19 out of 25 patients (76.0%) after the treatment. Preoperative serum PRL levels, age of patients at surgery, duration of galactorrhea, history of nursing, severity of galactorrhea and serum estradiol or progesterone levels had no correlation with cessation of galactorrhea. Ovulation was restored in 18 of 30 patients (60.0%) after the treatment and pregnancy was established in 12 patients. The PRL levels where ovulation was restored ranged from there to 57 ng/ml. The normal PRL levels did not inevitably ensure restoration of ovulation. There was no difference in the frequency of restoration of ovulation after the treatment between patients with preoperative PRL levels below 200 ng/ml after surgery. There was a prevalence in the frequency of restoration in amenorrhea Grade I, preoperative duration of sterility of less than 5 yr, microadenomas, a longer postoperative interval normal serum basal LH levels and peak LH levels in response to LH-RH and the presence of positive feedback control to surge LH in response to estrogen. Age of the patients at surgery, elevated dopamine activity in the hypothalamus and serum estradiol or progesterone levels were not correlated with restoration of ovulation. (36 Refs) (In JPN)

8. HYPERPROLACTINEMIA: THE EXPERIENCE AT THE UNIVERSITY OF KANSAS MEDICAL CENTER.

Silver BJ, Schimke RN, Kyner JL, Lukert BP, Bolinger RE, Meek JC
Dept. Medicine, Div. Metabolism, Endocrinology and Genetics, Univ. Kanasas Sch. Medicine-Kansas City, 39th and Rainbow Blvd., Kansas City, KS, 66103
J Kans Med Soc; 83(3):130-133,142 1982

Hyperprolactinemia was identified as being caused by prolactin (PRL)-secreting pituitary tumors in 21 women, on the basis of extensive endocrine tests. All patients had amenorrhea (primary in 2/21, secondary in 19/21) and 18/21 presented with galactorrhea. Sellar tomography disclosed abnormal sellar contours in 16/21 patients. Serum PRL levels and the results of pituitary function tests were similar in the patients showing normal and abnormal sellar contours. Transsphenoidal hypophysectomy (hypox) was performed in 14/21 patients. The other 7/21 declined hypox, and 4/7 were lost to follow-up. After hypox, serum PRL levels returned to normal in 8/14 patients, and 5/8 became pregnant. Two patients with persistent hyperprolactinemia showed normal PRL levels after bromocriptine (BCR) therapy was given; both became pregnant. Preoperative serum PRL levels tended to be lower in the patients whose PRL levels became normal after hypox than in the patients with persistent hyperprolactinemia, but the preoperative serum PRL value was an inconsistent predictor of the surgical outcome in individual patients. The complications of hypox were transient in all patients. It is concluded that the initial management of prolactinomas should be surgical, with pituitary irradiation (RT) and BCR for surgical failures. RT may be given if pregnancy is not desired. BCR cannot be advised as a substitute for surgery, and should not be begun until other potential causes of hyperprolactinemia have been ruled out by an extensive endocrine evaluation. (10 Refs)

9. APPROACH TO THE DIAGNOSIS OF HYPERPROLACTINEMIC STATES: THE NOMIFENSINE AND DOMPERIDONE TESTS.

Molinatti GM, Camanni F, Cocchi D, De Leo V, Genazzani AR, Massara F, Muller EE
Cattedra di Endocrinologia, Istituto di Medicina Interna dell'Universita, Corso Bramante, 10126 Torino, Italy
Panminerva Med; 23(1):5-10 1981

In the diagnosis of hyperprolactinemic states it is of clinical importance to distinguish patients who have prolactin-secreting microadenomas from those who have not. The authors have previously reported that Nomifensine (Nom) and Domperidone (Dom) may be successfully used as new tools for distinguishing functional from tumorous hyperprolactinemia; the present study describes the application of Nom to 93 hyperprolactinemic patients and, the comparison, made in 41 subjects, between prolactin responses to Nom and Dom. Patients were divided into: Group (A) Proven tumors; Group (B) Probable tumors;

Group (C) Hyperprolactinemia of uncertain etiology. Plasma prolactin values following administration of Nom and Dom were compared with those obtained from subjects with physiologic puerperal hyperprolactinemia. Administration of Nom did not significantly lower baseline plasma prolactin values in 42 patients with proven or probable tumor; in contrast the drug caused a prompt and clear-cut reduction in plasma prolactin levels in post-partum women and in 15 out of 51 patients with hyperprolactinemia of uncertain etiology. All but one of the latter showed a radiologically normal sella turcica and eight had regular menses or only polymenorrhea or oligomenorrhea. In the remaining 36 patients prolactin responsiveness to Nom was indistinguishable from that of the tumor groups; these patients presented with alterations of the sella turcica, plasma prolactin levels higher than 100 ug/ml and amenorrhea. Dom was administered to 41 hyperprolactinemic patients belonging to the above-mentioned groups; this study showed a homogeneity between prolactin responsiveness to Nom and Dom in 36 patients. From the overall findings it would appear that application of Nom and Dom may be of considerable help in the diagnosis of pathologic hyperprolactinemia. (17 Refs)

10. TUMOR GROWTH INHIBITION IN PATIENTS WITH PROSTATIC CARCINOMA TREATED WITH LUTEINIZING HORMONE-RELEASING HORMONE AGONISTS.

Tolis G, Ackman D, Stellos A, Mehta A, Labrie F, Fazekas AT, Comaru-Schally AM, Schally AV

Dept. Medicine, McGill Univ., Royal Victoria Hosp., Montreal, Quebec H3A 1A1, Canada

Proc Natl Acad Sci USA; 79(5):1658-1662 1982

Ten patients with prostatic carcinoma -6 with Stage C and 4 with Stage D disease were treated for 6 wk to 12 mo with agonistic analogues of luteinizing hormone-releasing hormone (LH-RH). [D-Trp6]LH-RH was given subcutaneously once daily at a dose of 100 ug and [D-Ser(But)6]des-Gly-NH210-LH-RH ethylamide (HOE 766) was given subcutaneously (50 ug once daily) or intranasally (500 ug twice daily). In all patients, mean plasma testosterone levels showed a 75% suppression by the 3rd wk of treatment and remained low thereafter. This was followed by a decrease or normalization of plasma acid phosphatase levels by the 2nd mo of treatment and a 47% decrease in serum alkaline phosphatase by the 10th wk of treatment in all but one patient. In patients with Stage C disease presenting with prostatism or urinary outflow obstruction, there was a noticeable clinical improvement. In two such patients, a decrease in the size of the prostate was confirmed by ultrasonography. In patients with Stage D disease manifested by diffuse bone metastases, there was relief of bone pain, and in one patient treated for greater than 12 mo the improvement was documented by radioisotope bone imaging. It is concluded that superactive agonistic LH-RH analogues hold promise as therapeutic agents in patients with androgen-sensitive prostatic adenocarcinoma. Furthermore, the analogues of LH-RH may be used to assess the responsiveness of patients to surgical castration. Long-term administration of LH-RH analogues could become an alternative to surgical castration and estrogen therapy for the treatment of hormone-dependent prostatic carcinoma. (Author abstract) (26 Refs)

11. RESPONSE TO LUTEINIZING RELEASING HORMONE, THYROTROPHIC RELEASING HORMONE, AND HUMAN CHORIONIC GONADOTROPHIN ADMINISTRATION IN HEALTHY MEN AT DIFFERENT RISKS FOR PROSTATIC CANCER AND IN PROSTATIC CANCER PATIENTS.

Hill P, Wynder EL, Garbaczewski L, Garnes H, Walker AR

American Health Foundation, Valhalla, NY, 10595

Cancer Res; 42(5):2074-2080 1982

A comparative study of the pituitary and testicular response to luteinizing releasing hormone (LHRH), thyrotrophic releasing hormone (TRH), and human chorionic gonadotrophin (HCG) administration was carried out in (a) low-risk young South African black and high-risk North American black men for prostatic cancer and (b) healthy elderly South African men and South African black men with prostatic cancer. A comparable HCG response occurred in young South African and North American black men, while a greater release of prolactin, but a lesser release of luteinizing hormone in response to LHRH:TRH occurred in South African black men. The response to HCG was comparable in elderly and young South African black men, although the prolactin release in response to TRH was greater in elderly men. A more prolonged release of luteinizing hormone was evident in men with prostatic cancer. Higher estradiol and estrone but lower androstenedione levels occurred in men with prostatic cancer. Data suggest that, in the elderly South African black men with prostatic cancer, estrogen metabolism is modified and that either the estrogen level or the higher estrogen:androgen levels modify the pituitary response to LHRH:TRH. A Western diet enhanced the changes in hormone profiles evident in black South African men with prostatic cancer. (Author abstract) (72 Refs)

12. PROBLEMS OF EARLY RECOGNITION OF SEMINOMA. IDENTIFICATION OF TUMOR CELLS IN TESTIS BIOPSIES OF 5 PATIENTS WITH OLIGOZOOSPERMIA.

Schutte B

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Andrologia; 13(6):521-534,536 1981

Five patients (25-34 yr old) underwent bilateral testis biopsies because of oligozoospermia. Abnormally small testes were presented bilaterally in three patients and unilaterally in the remaining two. One patient had elevated serum gonadotropin follicle stimulating hormone and luteinizing hormone. Testosterone and prolactin levels were normal in all five patients. No additional abnormal findings were present on examination or in the patients' histories. The specimens obtained at the biopsies were examined by both light and electron microscopy. In all samples, large cells with clear cytoplasm were observed near the basal membrane. The results of the histologic examinations led to final diagnoses of intratubular seminoma. Four of the patients underwent orchidectomy. Examination of the surgical specimens revealed the presence of seminoma cells throughout the organ. Early detection of seminomas is considered. The significance of age of the patient, findings of abnormally small testis without evidence of tumor by palpation, and occurrence of diminished spermatogenesis is considered. (26 Refs) (In GER)

13. PARADOXICAL HYPERSECRETION OF GROWTH HORMONE IN PATIENTS WITH ENDOMETRIAL ATYPICAL HYPERPLASIA AND CARCINOMA: EFFECT OF HYSTERECTOMY.

Ayalon D, Peyser MR, Limor R, Lessing JB, Ravid R
Inst. Reproductive Endocrinology, Dept. Obstetrics and Gynecology A, Municipal Governmental Medical Center, Univ. Tel Aviv, Tel Aviv, Israel
Gynecol Obstet Invest; 13(1):9-16 1982

Serum human growth hormone (HGH) levels and HGH responses to fasting glucose tolerance tests (GTT) were studied in 3 groups of age-matched postmenopausal women (53-65 yr old): 8 women scheduled for radical hysterectomy (hstx) for endometrial carcinoma (3/8) or atypical hyperplasia (5/8); 8 women scheduled for other gynecologic surgery for non-endometrial diseases; and 8 healthy women. None of the women was obese or diabetic. Baseline fasting glucose and HGH levels were normal in all groups. Urinary estrogen levels were within the normal postmenopausal range. The patients with endometrial neoplasms showed paradoxical HGH hypersecretion in response to GTT. When a repeat GTT was performed 6 mo after hstx, the paradoxical HGH reaction was absent. Since the controls awaiting surgery for non-endometrial diseases did not show a paradoxical HGH reaction to GTT, fasting and preoperative anxiety seemed to be ruled out as being responsible for the disturbance of HGH secretion in the patients with endometrial hyperplasia or cancer. The results suggested that the abnormal HGH responses might have been caused by some HGH-releasing factor in the malignant and premalignant endometrial tissues. (21 Refs)

14. EQUINE CUSHING'S DISEASE: PLASMA IMMUNOREACTIVE PROOPIOLIPOMELANOCORTIN PEPTIDE AND CORTISOL LEVELS BASALLY AND IN RESPONSE TO DIAGNOSTIC TESTS.

Orth DN, Holscher MA, Wilson MG, Nicholson WE, Plue RE, Mount CD
Div. Endocrinology, A-4215 Vanderbilt Medical Center North, Nashville, TN, 37232
Endocrinology; 110(4):1430-1441 1982

Equine Cushing's disease is almost invariably caused by ACTH hypersecretion by adenomas of pars intermedia (PI). PI proopiolipomelanocortin (proOLMC) peptides, such as alphaMSH, betaMSH, corticotropin-like intermediate lobe peptide (CLIP), and beta-endorphin (betaEND), are also secreted. In two horses with Cushing's disease, basal plasma immunoreactive ACTH was elevated about the same as in human Cushing's disease, but alphaMSH, betaMSH, CLIP, and betaEND were disproportionately increased. In the mare with more severe disease, neither low nor high dose dexamethasone suppressed hormone levels; in the less affected mare, high dose dexamethasone suppressed peptide levels only modestly, and cortisol never fell below normal. Both mares had glucose intolerance. Insulin did not lower blood glucose in the mare with severe Cushing's disease and diabetes mellitus; in the other, there was little response of peptides or cortisol, although blood glucose fell to 34 mg/dl. The adrenal cortices of both animals responded to exogenous ACTH. The less affected mare was studied further. The results suggest that proOLMC peptide secretion by a PI adenoma causing equine Cushing's disease is under similar control as normal PI in other species. Glucocorticoids, which suppress pars distalis (PD) but not PI secretion, and vasopressin and hypoglycemia, which stimulate PD but not PI secretion, had little or no effect on PI tumor proOLMC secretion; in contrast, dopamine, which inhibits PI but not PD proOLMC peptide secretion, also inhibited PI tumor secretion and thereby provides a potential rationale for treating Cushing's disease in horses. (55 Refs)

15. CIRCULATING ACTH AND RELATED PEPTIDES IN LUNG CANCER.

Ratcliffe JG, Podmore J, Stack BH, Spilg WG, Gropp C
Univ. Dept. Chemical Pathology, Hope Hosp., Salford M6 8HD, England
Br J Cancer; 45(2):230-236 1982

The prevalence of high levels of circulating ACTH-like immunoactivity was determined in 134 patients with lung cancer, using reference ranges from 52 age- and sex-matched patients with non-malignant lung disease. Two studies used ACTH radioimmunoassays with different specificities. Study A used an unextracted plasma or serum assay for total ACTH immunoactivity. High serum ACTH levels occurred in 24% of patients with small-cell carcinoma and 3% of patients with non-small-cell cancer. In patients with small-cell carcinoma, levels were high in 12% with limited disease and 32% with extensive disease. Study B used an ACTH assay after plasma extraction by porous glass, which measured mainly regular 1-39 ACTH. Here no lung-cancer patient had levels above the reference range, suggesting that the high levels in Study A may be due to plasma ACTH components which are poorly extracted by porous glass. It is concluded that high circulating ACTH immunoactivity occurs in a minority of patients with lung cancer, particularly those with extensive small-cell carcinoma. Indirect evidence suggests that the high ACTH levels detected with assays for total ACTH are due to molecular forms other than 1-39 ACTH, probably high-mol wt species. (Author abstract) (18 Refs)

16. ECTOPIC HORMONE FORMATION IN MULTIPLE ENDOCRINE TYPE IIA NEOPLASIA.

Weber T, Cordes U, Eberle S, Rothmund M, Krause U, Beyer J
Abteilung fur Innere Medizin, Endokrinologie und Stoffwechsel, Universitat Mainz, Langenbeckstr. 1, 6500 Mainz 1, W. Germany
Dtsch Med Wochenschr; 107(7):252-256 1982

A patient with high-grade osteoporosis had elevated levels of ACTH, cortisol and carcinoembryonic antigen (CEA). Computed tomography demonstrated enlarged adrenal glands. Despite intensive search no ACTH-producing tumor was found. A central Cushing's syndrome was thus possible, and a radiologically normal sella turcica made a microadenoma of the hypophysis a possibility. However, a one-time hypertensive crisis with elevated catecholamines raised the suspicion of an additional pheochromocytoma and thus provided the first pointer to a multiple endocrine neoplasia. Bilateral pheochromocytomas, discovered at adrenalectomy, as well as raised serum-calcitonin levels, strongly suggested coexistence of a C-cell carcinoma, which previously had not been demonstrated either by thyroid scanning or fine-needle biopsy. A total thyroidectomy revealed a multifocal and metastasizing C-cell carcinoma. On extraction it contained a high concentration of calcitonin, typical for a C-cell carcinoma. An unusual finding was of ACTH in extracts of both the C-cell carcinoma and the pheochromocytoma. It was immunologically identical with the the synthetic ACTH used as a standard. (Author abstract) (30 Refs) (In GER)

17. GASTRIN RESPONSES TO A TEST MEAL IN PATIENTS WITH FAMILIAL MEDULLARY THYROID CARCINOMA.

O'Dorisio TM, Falko JM, Cataland S, Almoney RW, George JM, Mazzaferri EL, Reynolds JC
Div. Endocrinology, Ohio State Univ. Hosp., 410 West 10th Ave., Columbus, OH, 43210
J Clin Endocrinol Metab; 54(4):798-802 1982

The serum gastrin response to a standard test meal was evaluated in patients with familial medullary thyroid carcinoma (MTC) and in normal subjects. Patients with MTC and elevated plasma calcitonin levels had a lower gastrin response to the test meal than did normal persons or MTC patients who had normal calcitonin levels postthyroidectomy. There was no significant difference between the mean gastrin response of the normal group and that of the MTC patients with normal calcitonin levels. The serum gastrin response was studied before and after thyroidectomy in four patients. In all four, the postoperative response was greater than the preoperative one. We conclude that patients with MTC may have reduced gastrin responses to a test meal. This effect may be related to circulating calcitonin, somatostatin, or other factors related to familial MTC. (Author abstract) (18 Refs)

18. HYPERCALCEMIA IN CANCER.

Bull FE
Dept. Internal Medicine, Univ. Michigan Medical Center, Ann Arbor, MI
Oncologic Emergencies. Yarbro JWand Bornstein RS, ed. New York, Grune and Stratton, Clinical Oncology Monographs, 430 pp., 1981.

Clinical aspects, pathogenesis, and treatment of hypercalcemia (HC) in cancer patients are discussed. Renal, gastrointestinal, CNS, and cardiovascular effects of HC are described. The roles of parathyroid hormone, prostaglandins, osteoclastic activating factor, and other factors in the development of HC in cancer patients is considered. Treatment of HC may include hydration, diuretics, dialysis, calcitonin, mithramycin, inorganic phosphate, corticosteroids, antiprostaglandin therapy, and other measures. Acute and chronic management of HC is described. (63 Refs)

19. RADIOIMMUNOASSAY FOR THE MIDDLE REGION OF HUMAN PARATHYROID HORMONE USING AN HOMOLOGOUS ANTISERUM WITH A CARBOXY-TERMINAL FRAGMENT OF BOVINE PARATHYROID HORMONE AS RADIOLIGAND.

Mallette LE, Tuma SN, Berger RE, Kirkland JL
c/o Dr. L. E. Mallette, Medical Service (111E), Veterans Admin. Medical Center, 2002 Holcombe Blvd., Houston, TX, 77211
J Clin Endocrinol Metab; 54(5):1017-1024 1982

A new type of RIA for human parathyroid hormone (hPTH) is described. The antiserum was generated in a goat against hPTH, and the radioligand is a carboxy-terminal fragment of bovine PTH (bPTH). Although the antiserum is bivalent, use of the fragment as tracer yields an assay monospecific for the midregion of the PTH molecule. The assay can detect 0.3 fmol/tube of intact hPTH-(1-84) or 0.1 fmol synthetic hPTH-(44-68), but does not detect hPTH-(1-34), hPTH-(53-84), or bPTH-(28-48). Immunoreactive PTH (iPTH) was detectable in 85 of 92 normal subjects, with a normal range of about 0.1-0.5 microU/ml hPTH Research Standard 75/549. iPTH was undetectable in 22 consecutive severely hypoparathyroid patients and was above normal in 147 of 158 patients with primary hyperparathyroidism. In 60 patients with nonparathyroid hypercalcemia, iPTH averaged 20% lower than in normal subjects, but was still detectable in 80%. Mean iPTH values in hypercalcemia due to malignancy or other nonparathyroid causes were indistinguishable. When renal insufficiency supervened in those with nonparathyroid hypercalcemia, iPTH tended to increase, and reached levels three- to four-fold above normal when serum creatinine was above 5 mg/dl. In chronic renal failure, iPTH levels were 5-to 36-fold above normal in patients just beginning hemodialysis and 60-to 600-fold evaluated in those with severe osteitis fibrosa. The distribution of iPTH values in hypercalcemic chronic hemodialysis patients was bimodal; values were about 600-fold elevated in patients whose hypercalcemia responded to parathyroidectomy (tertiary hyperparathyroidism), but only 2-to 20-fold increased in those with nonparathyroid hypercalcemias. The assay was sensitive enough to detect changes that occurred spontaneously in normal subjects or were induced by EDTA infusion. The assay was also useful in detecting venous PTH. This new assay, with its excellent sensitivity, provides a useful diagnostic and research tool for studies of human parathyroid function. (Author abstract) (33 Refs)

20. USEFULNESS AND LIMITATIONS OF DETERMINATION OF SERUM PARATHORMONE IN DIAGNOSIS OF PRIMARY HYPERPARATHYROIDISM.

Esbrit P, Rapado A
Unidad Metabolica, Fundacion Jimenez Diaz, Madrid, Spain
Rev Clin Esp; 163(3):173-177 1981

Thirty-one patients (13 males, 18 female; 13-66 yr old) had primary hyperparathyroidism (HPP), which manifested itself in 18 of the patients by nephrolithiasis symptoms, in 10 by symptomatic hypercalcemia, and in 3 by fibrous and cystic osteitis. Histologic diagnosis indicated parathyroid adenoma in 24 of the patients and hyperplasia in 7. Two different radioimmunoassays (with C-terminal and N-terminal) were used to determine parathyroid hormone (PTH). Ca serum levels were 10.3-13.5 mg/deciliter (dl), for Mg were 1.2-2.4 mg/dl, for PO4 were 1.3-3.9 mg/dl, for PTH C-terminal were less than 300-14,000 picog/ml, and 66-500 picog/ml for PTH N-terminal. Results of PTH C-terminal were elevated in 22/26 patients. PTH C-terminal and Ca results were correlated in 16 of the patients. PTH N-terminal results were less valuable and useful in the interpretation of HPP, than results obtained for PTH C-terminal. (35 Refs) (In SPA)

21. INCREASED ABSOLUTE CALCIUM BINDING TO ALBUMIN IN HYPOALBUMINAEMIA.

Besarab A, Caro JF
Thomas Jefferson Univ., Room 1014, Coll. Building, 1025 Walnut St., Philadelphia, PA, 19107
J Clin Pathol; 34(12):1368-1374 1981

The amount of calcium bound to protein was measured in 30 patients with differing diseases and varying degrees of hypoalbuminemia. Total serum calcium increased directly with both serum albumin and ultrafilterable calcium concentrations. The estimated amount of calcium bound per gram of albumin varied inversely with the albumin concentration, decreasing from 2.0 to 1.0 mg calcium/g albumin as albumin concentration increased from 1.7 to 3.1 g/dl. Circulating parathyroid hormone (PTH) concentrations varied inversely with measured ultrafilterable calcium concentrations. The frequency of raised PTH concentrations decreased as serum albumin increased. Use of a conventional correction factor for albumin binding (0.88 mg calcium bound per gram of albumin) to calculate corrected total calcium led to major errors in estimating ultrafilterable calcium in these patients. The PTH concentrations in turn correlated with the degree of deviation between estimated and measured ultrafilterable calcium concentrations. Ionized calcium was low in seven of ten additional hypoalbuminemic patients studied whereas correction of total calcium for albumin indicted normocalcemia in all. Thus correction of total calcium in patients with hypoalbuminemia by formulae which use a fixed binding ratio of calcium to albumin may give an erroneous impression of normocalcemia. The increase in calcium binding ratio during hypoalbuminemia needs to be considered during assessment of calcium status in these patients. (Author abstract) (23 Refs)

22. HORMONAL CHANGES IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES.

Pavelic K, Pekic B, Gabrilovac J, Bratic-Mikes V, Boranic M
Dept. Experimental Biology and Medicine, Ruder Boskovik Inst., P.O. Box 1016, Bijenicka c. 54, 41001 Zagreb, Yugoslavia
Biomedicine [Express]; 35(6):181-184 1981

Levels of immunologically reactive insulin (IRI), growth hormone (GH), thyroxine, cortisol and ACTH in sera of patients with various hematological malignancies were determined. IRI and GH levels were increased in 80% of the patients regardless of the type of disease. IRI was more elevated in relapse than in remission. Cytostatic treatment returned IRI serum levels to normal. Thyroxine, ACTH and cortisol in serum were higher in only two percent of the patients with hematological malignancies. (Author abstract) (23 Refs)

23. THYROID AND ANTITHYROID DRUGS (SIDE EFFECTS).

Bouillon R
Lab. Experimental Medicine, Catholic Univ. Leuven, Rega Inst., Minderbroedersstraat 10, 3000 Leuven, Belgium
Side Eff Drug Annu; (5):381-385 1981

Side effects of thyroid hormones and antithyroid drugs are reviewed. Thyroid hormones are used for replacement therapy and have been associated with accidental intoxication. Use of antithyroid drugs during pregnancy and lactation and duration of treatment and prediction of relapse of hyperthyroidism are discussed. Iodine preparations in the perinatal period, radioactive iodine, and use of 131I in malignant thyroid tumors are reviewed. (36 Refs)

24. SERUM SOMATOMEDIN ACTIVITY IN CHILDREN AFTER SURGERY FOR CRANIOPHARYNGIOMA.

Martinez MJ, Chaussain JL, Schimpff RM, Donnadieu M, Roger M, Job JC
(c/o Chaussain) Laboratoire de Recherches sur la croissance, INSERM U 188, Hopital Saint-Vincent-de-Paul, 74, avenue Denfert-Rochereau, 75014 Paris, France
Arch Fr Pediatr; 38(Supplement1):881-886 1981

Somatomedin (ST) activity and blood hormone levels were studied in 22 children (10 males, 12 females; 5-15 yr old) who had undergone surgery for craniopharyngiomas. The patients exhibited varying rates of growth. Serum growth hormone levels were consistently less than 1 nanog/ml. The correlation between serum ST activity and the speed of growth showed a highly significant correlation. No correlation was observed between serum ST activity and other clinical parameters: percentage of excess wt and recent variations in wt. No correlation was found between ST activity and blood concentrations of insulin and prolactin. A negative correlation between ST activity and plasma cortisol levels was observed when only patients not receiving hydrocortisone therapy were considered; among these patients, a negative correlation was also found in comparing serum cortisol and growth rate. When the total group of patients was considered no such negative correlations were noted. Patients receiving thyroid hormones showed a positive correlation between ST activity serum concentrations of triiodothyronine and thyroxine. Triiodothyronine levels were positively correlated with the rate of growth. The results indicated that in children operated on for craniopharyngioma, growth is related to a generation of ST independent of growth hormone secretion and is closely controlled by endogenous secretions of cortisol and thyroid hormones. (15 Refs) (In FRE)

25. PLASMA SOMATOSTATIN IN NORMAL SUBJECTS AND IN VARIOUS DISEASES: INCREASED LEVELS IN SOMATOSTATIN-PRODUCING TUMORS.

Saito H, Saito S
Dept. Lab. Medicine, Sch. Medicine, Univ. Tokushima, 2-50 Kuramoto-Cho, Tokushima 770, Japan
Horm Metab Res; 14(2):71-76 1982

The plasma levels of somatostatin (SRIF) were studied in normal subjects and patients with various disorders by a sensitive and specific radioimmunoassay. In 45 normal subjects, the fasting plasma SRIF concentrations were 13.3 +-5.3 pg/ml (mean +- SD). Very high concentrations of plasma SRIF, ranging from 125.0 pg/ml to 400.0 pg/ml, were found in all four patients with medullary carcinoma of the thyroid examined and the SRIF levels were changed in parallel with their clinical course after resection of the tumor. A case of pheochromocytoma also showed a relatively high SRIF concentration in plasma (47.0 pg/ml), but the plasma SRIF level decreased to 8.7 pg/ml after removal of the tumor. In normal subjects, plasma SRIF levels did not fluctuate during 2 hr-observation period in basal state. Glucagon (1 mg, iv) and secretin (3 CHRU/kg BW, iv infusion over 30 min) had no effect on the SRIF levels in the peripheral blood plasma of normal subjects. On intravenous infusion of arginine (0.5 g/kg BW) over 30 min, all six normal subjects showed a significant increase in plasma SRIF 30-45 min after the start of the infusion (basal value, 11.6 +-1.5 pg/ml; peak value, 27.2 +-3.0 pg/ml; p less than 0.005). Two cases of medullary thyroid carcinoma showed exaggerated responses after the arginine administration (increases of 103 pg/ml and 157 pg/ml, respectively), suggesting that SRIF was released from the tumor. These findings indicate that plasma SRIF determination in the basal state and after arginine administration is useful for detecting and following up SRIF-producing tumors. (Author abstract) (32 Refs)

26. PLASMA INSULIN AND C-PEPTIDE DYNAMICS IN VARIOUS DISEASES OF THE LIVER.

Obayashi M, Kawakami H, Hashimoto H, Nakanishi T, Miyoshi A
First Dept. Internal Medicine, Hiroshima Univ. Sch. Medicine, Hiroshima, Japan
Naika Hokan; 28(11):323-337 1981

Changes in blood sugar (BS) and immuno-reactive insulin (IRI) dynamics of patients with various liver diseases were compared with those in normal adults and patients with primary diabetes. Oral glucose tolerance tests (OGTT; 50 g glucose) were performed in 157 cases (14 acute hepatitis, 30 chronic hepatitis, 62 liver cirrhosis, 28 primary hepatic cancer, 11 metastatic liver cancer, and 12 alcoholic hepatopathy) and allergin tolerance tests (ATT) were performed in 51 cases (35 liver cirrhosis, 10 primary hepatoma, and 6 metastatic hepatoma). Prior to and following the OGTT, IRI levels were 09.0 +-7.3 microunits(uU)/ml (before OGTT), 34.7 +-33.7 (min

30), 54.1 +-45.7 (min 60), 54.2 +-39.2 (min 120), and 26.3 +-15.5 (min 180) in the patients with primary hepatic cancer and were 6.9 +-4.1 uU/ml (before), 21.7 +-13.7 (min 30), 30.7 +-21.5 (min 60), 32.6 +-31.8 (min 120), and 21.6 +-18.6 (min 180) in the patients with metastatic liver cancer; all of the IRI levels in the primary liver cancer patients were higher than those of the metastatic cancer patients. Although the BS curves of the metastatic liver cancer patients were higher than those of the controls, IRI levels were markedly lower, and the IRI levels of both groups of liver cancer patients at min 30 after the OGTT were significantly lower than those of the normal controls. IRI levels of the patients who had primary liver cancer with complications of cirrhotic changes were significantly lower than those of the patients with cirrhosis alone. (29 Refs) (In JPN)

27. PARANEOPLASTIC ENDOCRINOPATHIES ASSOCIATED WITH NONRENAL GENITOURINARY TUMORS.

Altaffer LF
Dept. Urology, Naval Regional Medical Center, Camp Lejeune, NC
J Urol; 127(3):411-416 1982

The ectopic or inappropriate production of parathyroid hormone (PTH), catecholamines (CTA), serotonin (ST), human chorionic gonadotropin (HCGT), adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH), calcitonin, estrogens (ES), human placental factor (HPF), erythropoietin, insulin-like substances, and prostaglandins associated with various renal tumors is reviewed. Several case reports of apparent PTH secretion by urothelial tumors exist. In all of the cases resolution of the hypercalcemia followed definite treatment of the cancer. Diagnosis of pheochromocytoma is made by measuring elevated serum, urinary CTA and metabolites. Prognosis is generally good but long-term follow-up with urinary levels of CTA or the metabolites is recommended. Signs and symptoms of some carcinoid tumors are probably caused by excessive production of ST. The secretion of HCGT by testicular neoplasms is well known and the use of HCGT as a tumor marker is applied in practice. ACTH was identified in three cases of carcinoma of the prostate. In 1969, a case of carcinoma of the prostate with evidence of ectopic secretion of ADH by the neoplasm was reported. The secretion of a thyroid stimulating hormone-like substance has been reported in association with trophoblastic tumors in women and in two cases of testis tumors. The secretion of ES, androgens, pregnanediol, and luteinizing hormone, has been associated with Leydig cell tumors, gonadal stromal tumors, and gonadoblastomas. The identification of HPF in the syncytiotrophoblastic cells in malignant teratoma of the testis was reported in 1966. Hypoglycemia has been shown to be associated with a variety of extrapancreatic tumors. Hormonally active tumors frequently demonstrate undifferentiated or anaplastic histologic patterns and, in general, patients with hormonally active tumors appear to have a poor prognosis. (83 Refs)

28. INCREASED PLATELET CATECHOLAMINE CONTENT IN PHEOCHROMOCYTOMA: A DIAGNOSTIC TEST IN PATIENTS WITH ELEVATED PLASMA CATECHOLAMINES.

Zweifler AJ, Julius S
Div. Hypertension, Univ. Michigan Medical Center, Box 48, R 6669 Kresge Medical Res. Building, Ann Arbor, MI, 48109
N Engl J Med; 306(15):890-894 1982

Measurement of platelet catecholamine content in 16 patients (5 male, 11 female; 1-62 yr old) with suspected pheochromocytoma and elevated plasma catecholamine levels [norepinephrine greater than 650 picog (pg)/ml, epinephrine greater than 120 pg/ml] is reported. Catecholamine content was determined by radioenzymatic assay. Of the subjects, 10 with documented pheochromocytoma had significantly increased platelet catecholamine content. The remaining six patients had normal platelet catecholamine levels and no tumor. Following tumor removal, platelet catecholamines tended to return to normal more slowly than plasma catecholamines. Patients suspected of having pheochromocytoma on clinical grounds and who have plasma norepinephrine levels greater than 2000 pg/ml should be sent directly for localizing procedures. In patients suspected of pheochromocytoma and whose plasma norepinephrine concentration is elevated but less than 2000 pg/ml, determination of platelet catecholamine content may be a useful intermediate step in diagnosis. (17 Refs)

29. CHANGES OF CATECHOLAMINE LEVELS IN PATIENTS WITH HYPERTENSION DURING SURGICAL TREATMENT OF STOMACH AND RECTAL CANCER.

Frid IA, Evtiukhin AI, Aleksandrin GP, Bernshtein MI, Simonov NN, Paikin MD
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Vestn Khir; 128(1):120-124 1982

The effect of surgery on the catecholamine levels was studied in 41 stomach cancer patients and 30 rectal cancer patients with concomitant hypertension. The patients with stomach cancer underwent subtotal resection and the patients with rectal cancer underwent abdominal-anal resection or abdominal-perineal extirpation. Postoperative increase of the blood and urine levels of epinephrine and norepinephrine in the patients with concomitant hypertension was more pronounced than that in the patients without hypertension. (8 Refs) (In RUS)

30. USE OF CALF THYMOSIN IN TREATING ACUTE LEUKEMIA COMPLICATED WITH INFECTION.

Dept Internal Medicine
Tongren Hosp., Beijing, People's Republic of China
Zhonghua Neike Zazhi; 20(7):436-437 1981

Treatment of serious bacterial infections complicating acute leukemia is described for 12 cases. Thymosin fraction 5 (THF5) was extracted from the thymus gland of a 2-3-day-old male calf. After receiving THF5 (1-5 mg, sc, 1x daily, total dose 10-66 mg), six patients recovered, showing negative bacterial tests and normal or greatly improved T cell immune functions compared with patients who showed partial responses; one patient did not respond. (no Refs) (In CHI)

EFFECTS ON NORMAL AND NEOPLASTIC CELLS AND TISSUES

31. THE EFFECT OF PROLACTIN ON HUMAN ALDOSTERONE-PRODUCING ADENOMAS IN VITRO.

Carroll JE, Campanile CP, Goodfriend TL
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J Clin Endocrinol Metab; 54(4):689-692 1982

There is evidence for an unidentified aldosterone-stimulating factor of pituitary origin. We measured the effect of ovine

PRL (oPRL) on aldosterone secretion by isolated cell suspensions of human aldosterone-producing adenomas (APAs) and compared it to the effects of angiotensins, ACTH, and potassium (K+). In the first APA, the aldosteronotropic action of large doses of oPRL was double that of angiotensin II (AII); the response to ACTH was triple that to AII, while K+ had a small stimulatory effect. Results with the second APA showed that physiological concentrations of oPRL caused a response nearly double that to AII, but, once again, less than the response to ACTH; K+ was inert. ACTH contamination of the oPRL preparation was too minute to account for these findings. We conclude that oPRL possesses aldosterone-stimulating activity in APAs greater than that of angiotensins and potassium, but less than that of ACTH. These data suggest a role for PRL in aldosterone secretion by aldosterone-producing adenomas. (Author abstract) (19 Refs)

32. PROLACTIN STIMULATION OF ORNITHINE DECARBOXYLASE ACTIVITY IN CULTURED RAT MAMMARY TUMORS.

Frazier RP, Costlow ME
Dept. Biochemistry, St. Jude Children's Res. Hosp., Memphis, TN, 38101
Exp Cell Res; 138(1):39-45 1982

Ovine prolactin increased ornithine decarboxylase (ODC) activity in 13 of 14 primary cultures of 7,12-dimethylbenzanthracene-induced rat mammary tumors. The 27-436% increase (mean 219%) in ODC activity required a 3-hr incubation with at least 1,000 ng prolactin/ml. Lower prolactin concentrations were ineffective. Bovine fetal serum or other hormones were not required for the prolactin effect. Addition of dibuturyl cyclic AMP (db-cAMP) (2.5 mM) to cultures increased ODC activity two-fold, whereas dibuturyl cyclic GMP (db-cGMP) (2.5 mM) had little effect. When either nucleotide plus 10 or 100 ng prolactin/ml was added. ODC activity increased three- to four-fold. These results show that increased ODC activity is an early event in prolactin action in cultured rat mammary tumor cells. The cyclic nucleotides appear to be necessary for the cells to respond to physiologic levels of hormone. (Author abstract) (33 Refs)

33. EFFECT OF VASOACTIVE INTESTINAL POLYPEPTIDE ON GROWTH HORMONE SECRETION IN PERFUSED ACROMEGALIC PITUITARY ADENOMA TISSUES.

Chihara K, Iwasaki J, Minamitani N, Kaji H, Matsukura S, Tamaki N, Matsumoto S, Fujita T
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J Clin Endocrinol Metab; 54(4):773-779 1982

The effects of vasoactive intestinal polypeptide (VIP), dopamine, and somatostatin (SRIF) on GH secretion were examined in vitro in perfused pituitary adenoma tissues obtained at surgery from seven patients with acromegaly. The perfusion of VIP at 5 x 10(-8) M resulted in a significant increase in effluent GH levels in five of the seven adenomas. A dose-related GH response was observed from 5 x 10(-9) to 5 x 10(-7) M VIP in two adenomas examined. SRIF at 5 x 10(-8) to 10(-7) M suppressed not only baseline secretion of GH but also inhibited GH rises elicited by VIP in six of the seven adenomas. Dopamine at 5 x 10(-7) to 5 x 10(-6) M decreased the baseline secretion of GH in six of the seven adenomas. In four of the six adenomas responsive to dopamine, dopamine suppressed VIP-induced GH release when perfused simultaneously. In the remaining two dopamine-sensitive adenomas in which VIP alone failed to affect GH release, the inhibition by dopamine of GH release was blocked by VIP perfused concomitantly with dopamine. Synthetic TRH or theophylline perfused at the end of the experiment stimulated GH release in all of the adenomas, indicating the viability of tumor cells throughout the study. These results suggest that VIP stimulates GH release by its direct action on pituitary adenoma cells of acromegalic patients and that VIP, SRIF, and dopamine interact at the pituitary level in modulating GH secretion from these adenomas. (Author abstract) (32 Refs)

34. RESTORATION BY CYCLIC AMP OF THE DIFFERENTIATED PHENOTYPE OF CHONDROCYTES FROM DEDIFFERENTIATED CELLS PRETREATED WITH RETINOIDS.

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Mol Cell Biochem; 42(3):145-153 1982

Parathyroid hormone (PTH) increases the cyclic AMP level in rabbit costal chondrocytes in culture. PTH, dibutyryl cyclic AMP (DBcAMP), and 8-bromo cyclic AMP (8-Br cAMP) induce ornithine decarboxylase (ODC) and expression of the differentiated phenotype of chondrocytes in this cell system. On the other hand, retinoids inhibit expression of the differentiated phenotype of chondrocytes. In the present study, the effects of PTH, DBcAMP, and 8-Br cAMP on rabbit costal chondrocytes pretreated with retinoids were examined. PTH did not increase the cellular cyclic AMP level in de-differentiated cells that had been pretreated with retinyl acetate or retinoic acid for 3 days, but it did increase the cyclic AMP level 4 days after removal of retinoids. PTH did not stimulate ODC activity or expression of the differentiated phenotype of chondrocytes in the de-differentiated state. On the other hand, DBcAMP or 8-Br cAMP stimulated expression of the differentiated phenotype of chondrocytes even in de-differentiated cells, as judged by morphological and histological changes of the cells and increase in glycosaminoglycan synthesis. Cyclic AMP analogues also induced ODC in these cells. (Author abstract) (34 Refs)

35. SALMON THYROCALCITONIN EFFECT ON NEOPLASTIC BONE DISEASES.

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Istituto di Oncologia, Universita di Messina, Contrada Papardo-Sperone, 98010 Messina, Italy
Tumori; 68(1):63-66 1982

The therapeutic results obtained in 20 patients affected by bone metastases secondary to different neoplastic diseases, treated with synthetic Salmon calcitonin, are reported. The action on symptom 'pain' and on restoration of motor function was very good, as was the tolerance. The protective role of the drug was proved in a stabilizing action - ie, nonprogression - of the treated lesions (x-ray checking), and in the balancing effect on calcemia and other hematochemical parameters, even in progression of disease. (Author abstract) (20 Refs) (In ITA)

36. IMMUNOCHEMICAL AND BIOLOGICAL CHARACTERIZATION OF CALCITONIN ORIGINATING FROM TRANSPLANTED MEDULLARY THYROID CARCINOMA IN RATS.

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Dept. Physiology and Biochemistry, Dental Faculty, Univ. Oslo, Oslo, Norway

Acta Endocrinol (Copenh); 99(3):397-403 1982

The immunoreactive and biological activities of calcitonin (CT) produced by transplanted rat medullary thyroid carcinomas have been studied. Immunoreactive CT (iCT) in serum and in tissues of rats carrying tumors of generations 5-8 was characterized by gel filtration on Sephadex G-100 followed by radioimmunological measurements using region specific antiserum. The hypocalcemic effect of sera and tumor extracts was tested in a rat bioassay. Rats with transplanted of the fifth and sixth generations had mainly (70-84%) circulating iCT species of molecular size comparable to intact hormone. However, in rats with tumors of the seventh and eighth generations corresponding circulating iCT forms comprised less than 52% of total immunoreactivity while 32-38% eluted earlier. In comparison, iCT corresponding to intact hormone represented 30-50% of total immunoreactivity in the tumor extracts and no differences were observed between the generations. Sc injections of sera from rats and of tumor extracts reduced the serum levels of ionized calcium in test rats. The sera containing mainly intact iCT showed the strongest biological potency. We conclude that rat transplanted under the kidney capsule is able to secrete biologicaly active CT. However, the heterogeneity of circulating iCT increases in rats with transplanted tumors of older generations, approaching the heterogeneity of stored hormone in the gland. (Author abstract) (35 Refs)

37. THYROID INFLUENCE ON THE GROWTH OF HEPATOMA HW-165 IN WISTAR RATS.

Lemaire M, Baeyens W, De Saint-Georges L, Baugnet-Mahieu L

(c/o Baugnet-Mahieu) Radiobiology Dept., C.E.N./S.C.K., B-2400 Mol, Belgium

Biomedicine; 34(3):133-139 1981

The development of a fast-growing hepatoma (HW-165) in normal euthyroid Wistar rats, was shown to be stimulated by daily injection of a dose of triiodo-L-thyronine (T3) as low as 1.5 ug/100 g body wt. Administered to thyroidectomized rats, T3 completely restored the frequency of tumor initiation and accelerated the growth of the hepatoma, which had been considerably slowed down in hypothyroid rats. Contrary to other investigators, working on fast-growing Morris hepatomas, we did not observe any significant increase in the T3 level in the serum of hepatoma HW-165-bearing rats. Similarly, the tetraiodo-L-thyronine (T4) levels were of the same order of magnitude in the blood of both normal and tumor host animals. The mitotic activity was reduced in hepatomas transplanted in hypothyroid rats and increased in tumors of T3-treated animals. These results support the assertion of Short suggesting a relationship between the mitogenic effects of iodothyronines on the normal hepatocyte and on transplanted tumors of hepatic origin. (Author abstract) (20 Refs)

38. DECREASE IN TUMOUR GROWTH BY INJECTIONS OF HISTAMINE OR SEROTONIN IN FIBROSARCOMA-BEARING MICE: INFLUENCE OF H1 AND H2 HISTAMINE RECEPTORS.

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Br J Cancer; 45(1):54-60 1982

C3H and C57 BL/6 mice carrying methylcholanthrene-induced fibrosarcomas were injected ip daily with histamine, metiamide (anti-histamine Type-2 receptor), histamine + metiamide, mepyramine (anti-histamine Type-1 receptor), serotonin and methysergide (anti-serotonin). Inhibition of tumor growth and lengthened survival were observed with histamine and histamine + metiamide. The best results (both on tumor growth and survival) were obtained with serotonin. Survival was increased by metiamide and decreased by mepyramine and methysergide. In histamine-treated and in serotonin-treated mice, histological studies of the tumors showed large and numerous foci of hemorrhagic necrosis. Stimulation of histamine Type-1 or serotonin receptors and inhibition of histamine Type-2 receptors play a beneficial role in the host's defense against tumors. (Author abstract) (17 Refs)

39. THE DEGREE OF DIFFERENTIATION IN EARLY- AND LATE-ONSET FORMS OF PLATYFISH-SWORDTAIL HYBRID MELANOMAS: A MORPHOLOGICAL AND PHYSIOLOGICAL STUDY IN PRIMARY CULTURE.

Wakamatsu Y, Ozata K

Biological Lab., Yoshida Coll., Kyoto Univ., Kyoto 606, Japan

Dev Growth Differ; 23(3):263-271 1981

The degree of differentiation of melanomas in platyfish-swordtail hybrids was studied. Platyfish (Xiphophorus maculatus) were hybridized with swordtails (Xiphophorus helleri) to produced F1 hybrids. The hybrids were then backcrossed with swordtails to produce BC1 and BC2 generations. Hybridization produced two forms of cutaneous melanoma in the offspring: a fry form occurring usually in young fish and involving a large part of the body, and an adult form occurring in one or two primary sites in adult fish. Cell cultures were prepared from both types of melanoma and from normal skin. Cultures of normal skin contained few melanophores. A few melanophores attached to culture plates. Many of these melanophores had multiple, round or ovoid nuclei. Exposure to epinephrine induced complete melanosome aggregation within 5 min. The aggregation was reversible within 10 min of removal of epinephrine. Cultures of fry melanoma consisted mostly of melanoma cells that attached well to culture plates and became dendritic in culture. Approx 60% were mononucleate and most of the rest were binucleate. Epinephrine produced reversible melanosome aggregation in 80% of fry melanosomes. Adult melanoma cells were small and weakly pigmented; most were mononucleate. Epinephrine response varied from 0-80%. Epinephrine response was blocked in all cultures by dibenamine. Differences between normal, fry, and adult cultures reflected differences in cellular differentiation of melanophores and melanosomes. (28 Refs)

40. CELLULAR HETEROGENEITY IN THE LATE-ONSET FORM OF HEREDITARY MELANOMAS IN THE XIPHOPHORUS FISH HYBRIDS.

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Biological Lab., Yoshida Coll., Kyoto Univ., Kyoto 606, Japan
Dev Growth Differ; 23(3):273-285 1981

The late-onset form of melanomas which occur in the Xiphophorus hybrids (platyfish and swordtails) and carry a macromelanophore gene Sp, was examined for its cellular heterogeneity. The nodular melanomas used were removed from the body surface of fish aged 7-19 mo. The melanoma tissue were dissociated enzymatically and grown in culture. Cell size and shape, pigmentation, and response to epinephrine, were studied. Cells were varied in size, with variations in shape related to size. Development of dendrites also varied widely. Pigmentation was changing during the course of tumor growth and occurred independently of either cell size or shape. When cultures were treated with 10(-6) M epinephrine for 5-30 min, some cells showed rapid response by melanosome aggregation within 5 min while other cells did not respond within 30 min. There was no significant correlation between epinephrine responsiveness and cell size or cell shape. The stability of the various phenotypic traits was followed during the course of tumor growth. Cell size and shape were stable, but pigmentation and response to epinephrine varied. Results are discussed in relation to cell differentiation and tumor progression. (29 Refs)

EFFECTS OF ENDOGENOUS AND EXOGENOUS AGENTS ON NON-STEROID HORMONE ACTIVITY

41. CHARACTERIZATION OF THE DOPAMINERGIC REGULATION OF HUMAN PROLACTIN-SECRETING CELLS CULTURED ON EXTRACELLULAR MATRIX.

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J Clin Endocrinol Metab; 54(5):893-902 1982

Human PRL-secreting adenoma cells were cultured on an extracellular matrix (ECM) secreted by bovine corneal endothelial cells, and their sensitivity to dopamine and dopaminergic agonists was examined. Cells plated on ECM attach rapidly, adopt a flattened morphology, and maintain stable PRL secretion for several weeks. Dopamine inhibited PRL secretion from tumor and nontumor cells on ECM in a dose-dependent fashion, with IC50 values of 243 +-29 and 76 +-3.3 nM, respectively, and a maximal inhibition of 80% at 10(-5) M. Apomorphine (APO), dihydroergocryptine (DHE), and bromocriptine (CB-154) also inhibited PRL secretion from adenoma cells in a dose-dependent fashion, with IC50 values of 24 +-13, 0.35 +-0.1, and 0.05 +-0.01 nM, respectively. Thus, the rank order of potency of the dopamine agonists in inhibiting PRL secretion from adenoma cells was consistent with an interaction at a dopamine receptor: CB-154 greater than DHE greater than APO greater than dopamine. The dopamine antagonists, D-butaclamol, spiperone, domperidone, chlorpromazine, and l-butaclamol, reversed the inhibitory effect of DHE on PRL secretion with IC50 values of 0.8 nM, 0.9 nM, 1.3 nM, 80 nM, and 30 mu M, respectively. The inhibition of PRL secretion was stereoselective, since d-butaclamol was approximately 2,000 times more potent than the inactive l-isomer in reversing the effect of DHE. Pieces of adenomas incubated with dopamine before dispersion responded similarly to the dispersed cells plated on ECM, indicating that the ECM did not appear to alter the dopamine-mediated inhibition of PRL. In summary, human PRL-secreting adenoma cells cultured on ECM respond to dopamine in a dose-dependent fashion, but with an IC50 slightly greater than that observed with normal mammotrophs. The rank order of potency of the dopamine agonists to inhibit PRL secretion (CB-154 greater than DHE greater than APO greater than dopamine) and the rank order of potency of the dopamine antagonists to reverse the inhibitory effect of DHE (d-butaclamol approx spiperone greater than or equal to domperidone greater than chlorpromazine greater than l-butaclamol) are consistent with an interaction at a dopamine receptor and correlate with the ability of these agents to displace [3H]DHE in membrane-binding preparations. These data would argue that human PRL-secreting adenoma cells possess a dopamine receptor, both of high affinity and stereoselective, which mediates the inhibition of PRL secretion. (Author abstract) (39 Refs)

42. HYPOTHALAMIC-PITUITARY FUNCTION FOLLOWING BROMOCRIPTINE THERAPY IN PATIENTS WITH PROLACTINOMAS.

Badawy SZ, Notman DD, Sunderlin FS, Springer JM, Streeten DH, Omar MM, Marshall LD
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J Reprod Med; 27(3):139-145 1982

The hypothalamic-pituitary system was evaluated in 18 women (20-37 yr old) with prolactinomas prior to and 6 mo after therapy with bromocriptine (BR: 5 mg/day) in order to determine the effect of BR on the pituitary hormonal reserve function. After treatment, the prolactin response to thyroid-releasing hormone stimulation was significantly less than before treatment, although the percent max increment was higher. Serum prolactin levels fell to within normal levels in 73% of patients by wk 4 and in 95% by wk 12. Seven pregnancies occurred while the patients were taking BR. (29 Refs)

43. PARTIAL PURIFICATION FROM HEPATOMA CELLS OF AN INTRACELLULAR SUBSTANCE WHICH MEDIATES THE EFFECTS OF INSULIN ON PYRUVATE DEHYDROGENASE AND LOW KM CYCLIC AMP PHOSPHODIESTERASE.

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Arch Biochem Biophys; 215(1):339-344 1982

An enzyme-stimulating factor was isolated from hepatoma cells. The factor stimulated pyruvate dehydrogenase (PD) and low Km cyclic AMP phosphodiesterase in a dose-dependent fashion. PD stimulation was sodium-sensitive. The factor was similar to the second messenger of insulin derived from other cell types in acid stability, mol wt, insulin-dependent generation, and elution from the anion-exchange resin AG 1-X8 at an ionic strength of 0.4 M. (21 Refs)

44. THE ROLE OF ENDOGENOUS GASTRIC INHIBITORY POLYPEPTIDE IN THE ENTEROINSULAR AXIS.

Takemura J, Seino Y, Yamamura T, Tsuda K, Seino S, Itoh N, Imura H
c/o Dr. Jiro Takemura, Kyoto University School of Medicine, 54 Shogoin Kawahara-cho, Kyoto 606, Japan
J Clin Endocrinol Metab; 54(5):909-913 1982

In order to elucidate the relationship between the release of gastric inhibitory polypeptide (GIP) and insulin, we compared plasma GIP and insulin concentration responses to meal ingestion in normal subjects and patients with various surgical modifications of the food pathway. Nine patients with Billroth I partial gastrectomy (BI), seven patients with Billroth II partial gastrectomy (BII), and six patients with total gastrectomy (TG) were tested. In BI patients the increase in blood glucose was similar to that in normal subjects, but the response was significantly greater in BII and TG patients. In TG patients blood glucose rose significantly higher in response to a standard meal than in all other groups. In BI patients the mean peak GIP level after meal ingestion was significantly higher than in normal subjects. In BII and TG patients an extremely exaggerated GIP response after the meal was observed. The insulin response to feeding was increased only in the BII and TG patients. Since the insulin response was enhanced only when both the glucose and GIP responses were magnified, we conclude that endogenous GIP is a glucose-dependent insulinotropic factor. In addition, from the fact that meal-stimulated GIP release is most marked in patients with total gastrectomy, we conclude that the direct contact of food with the GIP-producing cells is a strong mechanical or chemical stimulus for GIP release. (Author abstract) (24 Refs)

RECEPTOR/ BINDING SITES

45. DOWN-REGULATION OF INSULIN RECEPTORS IN PRIMARY CULTURES OF R3230 AC RAT MAMMARY ADENOCARCINOMA CELLS.

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Endocrinology; 110(4):1155-1163 1982

Binding of insulin and Concanavalin A to primary cell cultures of the R3230AC rat mammary adenocarcinoma was studied as a function of time in culture. As the culture became confluent, the amount of insulin binding per cell increased with culture time and reached a plateau, whereas the binding of Con A to surface glycoproteins decreased to 50% of the initial value. Exposure of confluent cultures to insulin at 37 C resulted in down-regulation of the cell surface insulin receptors. The decrease in insulin binding was related to the ambient insulin concentration and the decreased numbers of receptors per cell with no apparent alteration in their affinity. The maximal decrease in receptor number was 60-70%. Cell cultures degraded significant amounts of insulin at 37 C, but the addition of bacitracin to the culture medium decreased the amount of degradation and increased the extent of down-regulation at each insulin concentration. Porcine proinsulin was less effective than insulin in competing with 125I-labeled insulin and inducing receptor down-regulation. Down-regulation of insulin receptors did not require protein synthesis. The rate of insulin-induced receptor loss was much faster than the decrease in insulin binding due to inhibition of protein synthesis by cycloheximide. The estimated half-life of the insulin receptor was 10.5 hr. Down-regulation of insulin receptors was reversible; regeneration of receptors to 50% of control levels occurred approx 9.6 hr after the removal of insulin and required protein synthesis. The results indicate that these mammary tumor cells retain the ability to regulate their insulin receptors. (Author abstract) (53 Refs)

46. GLUCOCORTICOIDS DOWN-REGULATE SOMATOSTATIN RECEPTORS ON PITUITARY CELLS IN CULTURE.

Schonbrunn A
Lab. Toxicology, Dept. Physiology, Harvard Sch. Public Health, Boston, MA, 02115
Endocrinology; 110(4):1147-1154 1982

Treatment of GH4C1 cells, a clonal strain of rat pituitary tumor cells which synthesize and secrete PRL and GH, with 5 x 10(-6) M cortisol caused a time-dependent decrease in [125I-Tyr1]SRIF-specific binding. Receptor affinity was the same in control and cortisol-pretreated cells, but the number of SRIF-binding sites decreased from 21,900 to 15,200 receptors/cell. Pretreatment of cells with 5 x 10(-7) M dexamethasone (1,4-pregnadien-9-fluoro-16alpha-methyl 11beta,17alpha,21-triol-3,20-dione) for 43 hr caused the same maximal decrease in [125I-Tyr1] somatostatin (SRIF)-specific binding as 5 x 10(-6) M cortisol; however, dexamethasone was 10x more potent than cortisol. Pretreatment of GH4C1 cells for 43 hr with 5 x 10(-6) M 17beta-estradiol, 17alpha-methyltestosterone, testosterone, or progesterone had no effect on [125I-Tyr1]SRIF-specific binding, indicating that this effect was glucocorticoid specific. Treatment of GH4C1 cells with both dexamethasone and cycloheximide caused the same decrease in [125I-Tyr1]SRIF-specific binding as did either agent alone. In contrast, the down-modulation of SRIF receptors by chronic TRH treatment was previously shown to be additive with cycloheximide. However, maximal concentrations of TRH and cortisol added together had no greater effect on SRIF receptors than TRH alone. Therefore, even though the effects of TRH and cortisol are differentially sensitive to cycloheximide, the pathways by which they down-regulate SRIF receptors probably overlap at a common rate-limiting step. In conclusion, the receptors for TRH and SRIF are modulated in opposite directions on GH4C1 cells by chronic glucocorticoid treatment. Since these two hypothalamic peptides have opposing effects on hormone release, such receptor modulation may play an important role in regulating pituitary responsiveness to these hypothalamic regulatory factors. (45 Refs)

47. VARIATION OF ALPHA-MSH RECEPTIVITY BETWEEN MALIGNANT MELANOCYTES FROM HORIZONTAL AND VERTICAL GROWTH PHASES IN A HUMAN SUPERFICIAL SPREADING MELANOMA.

Legros F, Coel J, Gossuin A, Lejeune FJ
Laboratoire de Physiopathology, Free Univ. Brussels, 2 rue Evers, 1000 Brussels, Belgium
Protides Biol Fluid Proc Colloq; 29:551-554 1982

Comparative alpha-melanophore-stimulating hormone (aMSH) receptivity was studied in the horizontal (HGP) and vertical (VGP) growth phases of malignant melanocytes from a human superficial spreading melanoma and in tissue sections from the same tumor. In the HGP, approx 10-15% of cells exhibited aMSH receptivity, compared to none of the cells in VGP. These results are related to Clark's hypothesis of mutational changes between the two phases. (5 Refs)

48. 125I-ALPHA-MSH BINDING IN HUMAN MELANOMA CELL LINES.

Gossuin A, Ghanem G, Temmerman A, Coel J, Henry PE, Legros F
Laboratoire de Physiopathology, Free Univ. Brussels, 2 rue Evers, 1000 Brussels, Belgium
Protides Biol Fluid Proc Colloq; 29:555-558 1982

Quantitative and qualitative hormone fixation to cultured human melanoma cells was studied with 125I-labeled alpha-melanophore-stimulating hormone (aMSH). Immunocytochemical and autoradiographic reactions demonstrated aMSH binding to a limited number of cultured human melanoma cells. The variability of receptive properties between two cell lines, IJB792 and IGR221, from sc metastases of two different patients was demonstrated; the two cell lines differed in the proportion of receptive cells, the number of cell receptors, and their apparent affinity constant. (12 Refs)

49. RECEPTORS FOR REGULATORY PEPTIDES IN EPITHELIAL GUT CANCER.

Forgue-Lafitte ME, Laburthe M, Zweibaum A, Rosselin G
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Protides Biol Fluid Proc Colloq; 29:595-598 1982

Studies on receptors for regulatory peptides, such as insulin and vasoactive intestinal peptide (VIP) in transformed gut epithelial cell lines from humans are reviewed. The coupling of insulin and VIP with their specific receptors triggers regulatory events: insulin regulates long-term effects (protein, RNA, and DNA synthesis), while VIP regulates events leading to glycogenolysis by activation of adenylate cyclase, cyclic AMP-dependent protein kinases, and phosphorylase a. Insulin is effective at very low concentration (10(-10) M). It was demonstrated that transformed cells of the digestive tract possess specific receptors for regulatory peptides which make them sensitive to their neuroendocrine environment. The insulin effect was not uniform; even in the same type of cell, the effect on growth can vary according to the batch of serum used. These receptors are coupled to a biological activity, the magnitude of which varies according to the cell line. (30 Refs)

OTHER RELATED STUDIES

50. RECEPTOR FOR 1,25-DIHYDROXYVITAMIN D3 IN GH3 PITUITARY CELLS.

Haussler MR, Manolagas SC, Deftos LJ
Dept. Biochemistry, Coll. Medicine, Univ. Arizona, Tucson, AZ, 85724
J Steroid Biochem; 16(1):15-19 1982

To determine if receptors for 1,25-dihydroxyvitamin D3 have a regulatory role in specific pituitary cells, two cell lines derived from pituitary tumors were examined. Cytosol prepared from the GH3 rat pituitary tumor cell line, which produces growth hormone and prolactin in approximately equimolar ratios, was found to contain a receptor-like macromolecule that bound 1,25-dihydroxyvitamin D3 with specificity and high affinity (Kd = 2.9 x 10(-10) M). The GH3 cytosolic binding component sedimented at 3.3S in high-salt sucrose gradients and adsorbed to DNA-cellulose. Its elution profile from DNA-cellulose and other biochemical properties were indistinguishable from those of classical 1,25-dihydroxyvitamin D3 hormone receptors. The receptor was not present in the AtT-20 mouse pituitary tumor cell line, which elaborates ACTH, beta-endorphin, and beta-lipotropin. Results suggest that 1,25-dihydroxyvitamin D3 may have a central regulatory action on pituitary hormones that affect vitamin D metabolism. (28 Refs)

51. MONOCLONAL ANTIBODIES TO HUMAN PROLACTIN AND CHORIONIC SOMATOMAMMOTROPIN.

Ivanyi J, Davies P
Dept. Experimental Immunobiology, Wellcome Res. Lab., Beckenham, Kent, England
Protides Biol Fluid Proc Colloq; 29:855-860 1982

Basic characteristics of hybridoma-produced antibodies towards human prolactin (hPRL) and human chorionic somatomammotropin (hCS) are described. The QB1 anti-hPRL cell line was formed by fusion of spleen cells, from high-responder AB/H strain BALB/c mice immunized with hPRL, with NS1 non-secretor myeloma cells. Four hybridoma lines were derived from BALB/c mice immunized with hCS. The specificities of the anti-hPRL antibody QB1 and of hybridoma antibodies EB1, 2, 3, and 4 were determined. An antibody-antibody competition assay of anti-hCS monoclonal antibodies was performed. (27 Refs)

52. ANTIBODIES AGAINST TSH RECEPTOR IN GRAVES' DISEASE: EVALUATION BY RELEASE OF CAMP.

Gomez JM, Navarro MA, Pastor MC, Soler J
Endocrinology Section, Cuidad Sanitaria 'Principes de Espana', Barcelona, Spain
Protides Biol Fluid Proc Colloq; 29:571-574 1982

Release of cyclic AMP (cAMP) was used to evaluate antibodies against thyroid-stimulating hormone (TSH) receptor in 35 patients with active Graves' disease (GD: with or without previous antithyroid treatment), 27 with treated GD, 12 in remission of GD, 12 with multinodular goiter, 10 with primary hypothyroidism, 6 with thyroid cancer, and 84 controls. TSH antibodies were identified in at least 92% of patients with hyperthyroidism of GD and patients with active GD released a significantly greater amount of cAMP than controls and patients with GD in remission. (8 Refs)

53. IDENTIFICATION OF HUMAN THYMIC EPITHELIAL CELLS WITH ANTIBODIES TO THYMOSIN ALPHA IN MYASTHENIA GRAVIS.

Dalakas MC, Engel WK, McClure JE, Goldstein AL, Askanas V
NIH, Building 36, Room 5D06, Bethesda, MD, 20205
Ann NY Acad Sci; 377:477-485 1981

Thymosin-alpha1 (alpha1) is a potent thymic polypeptide hormone. Using anti-alpha1 antibodies, we applied indirect immunofluorescence to human normal thymus of different ages and to hyperplastic, thymomatous, and 'involuted' thymus of myasthenia gravis (MG) patients. Alpha1 was localized only in the epithelial cells, lying singly, grouped, in Hassell's corpuscles, and proliferated in thymomas. Whereas normal thymuses had fewer and weakly stained cells, MG thymuses had many strongly positive epithelial cells; this was more evident in thymomas. Germinal centers were unstained. 'Involuted' MG thymuses had small islands of brightly stained cells lying among the fatty tissue. In cultured thymuses from three MG patients, epithelial cells but not fibroblasts were brightly stained for alpha1. Our findings (a) demonstrate the location, and presumably the origin, of alpha1 to be the thymic epithelial cell; (b) suggest the possibility that excess alpha1, because of its known effect on T-lymphocyte maturation and transformation of precursors to helper T-cells, may act pathologically to facilitate and perpetuate the dysimmune mechanism in MG; (c) may partially explain the beneficial effect of thymectomy in MG patients of any age; and (d) indicate that epithelial cells may be autonomous for the production of alpha1 as evidenced by their alpha1-positivity in culture. (Author abstract) (36 Refs)

54. SCIRRHOUS ARGYROPHIL CELL CARCINOMA OF THE STOMACH WITH MULTIPLE PRODUCTION OF POLYPEPTIDE HORMONES, AMINE, CEA, LYSOZYME, AND HCG.

Tahara E, Ito H, Nakagami K, Shimamato F, Yamamoto M, Sumii K
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Cancer; 49(9):1904-1915 1982

Sixteen argyrophil cell carcinomas in 59 gastric scirrhous carcinomas were examined histologically, ultrastructurally, and immunohistochemically for polypeptide hormones, CEA, lysozyme, and HCG. In 9 of these 16 tumors, polypeptides such as gastrin, somatostatin, and glucagon were demonstrated. Six of these nine tumors contained all three hormones, and three of these six tumors also had argentaffin cells. In all of these 16 tumors CEA were observed. Eight of them had CEA, lysozyme, and acid mucin synchronously. Of the above six tumors containing three peptides, three produced focal HCG. Ultrastructurally, several types of secretory granules were noted. Histologically, these 16 tumors showed poorly differentiated adenocarcinomas or signet ring cell carcinomas. Macroscopically, generalized type was 11 and localized type 5. No hormonal syndrome was detected in any of the patients. It was suggested that these scirrhous argyrophil cell carcinomas of the stomach with the multifunction originate from totipotent immature cells of endodermal origin. (Author abstract) (46 Refs)

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Non-Steroid Hormones

SERIES CB24 No. 82/09

SEPTEMBER, 1982

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CHARACTERIZATION OF NON-STEROID

HE 20.3173/2:

HORMONES IN EXPERIMENTAL AND IN VITRO SYSTEMS

1. BIOSYNTHESIS OF RAT INSULINS I AND II: EVIDENCE FOR DIFFERENTIAL EXPRESSION OF THE TWO GENES.

Kakita K, Giddings S, Permutt MA
(c/o Permutt) Dept. Internal Medicine, Metabolism Div., Washington Univ. Sch. Medicine, 660 South Euclid Ave., St. Louis, MO, 63110
Proc Natl Acad Sci USA; 79(9):2803-2807 1982

The purpose of these experiments was to determine the relative content and biosynthetic rate of insulins I and II under various experimental conditions. The two insulins were quantitated by polyacrylamide gel electrophoresis, electrotransfer to nitrocellulose paper, photoaffinity crosslinking, and immunodetection with anti-insulin antibody and 125I-labeled protein A. The ratio (mean +- SEM) of insulins, I/II, was 1.2 +-0.2 in Wistar-Furth rats fasted for 4 days, 1.6 +-0.2 in normal rats, and 5.5 +-0.8 in growth hormone-tumor-bearing hyperinsulinemic rats (p less than 0.01). The increase in content of rat insulin I compared to II in the growth hormone-tumor-bearing animals was confirmed by radioimmunoassay of gel slices. To determine whether the differences in contents of rat insulins I and II in the hyperinsulinemic rats was due to increased biosynthesis or a different turnover rate, isolated rat islets were incubated in [3H]leucine for 4 hr with 5.5 mM or 16.0 mM glucose in the incubation medium. Glucose stimulated insulin biosynthesis greater than eight-fold. The ratio of synthesis of rat insulin I relative to II was 0.9 +-0.1 at 5.5 mM glucose and 9.8 +-3.3 (p less than 0.01) at 16.0 mM glucose. Therefore, under conditions that stimulate insulin biosynthesis, there was a marked preferential synthesis of rat insulin I relative to II. These studies suggest that the two rat insulin genes are expressed independently and that, under stimulatory conditions, there is preferential expression of the rat insulin I gene. (Author abstract) (35 Refs)

2. CONCOMITANT SECRETION OF CALCITONIN, BETA-ENDORPHIN AND ACTH FROM MEDULLARY THYROID CARCINOMA IN VIVO AND IN VITRO.

Lamberts SW, Hackeng WH, Visser TJ
Dept. Internal Medicine III, Erasmus Univ., Rotterdam, The Netherlands
Eur J Cancer Clin Oncol; 18(3):253-260 1982

The present study was performed to investigate the possible synthesis of a common precursor molecule for calcitonin (CT), adrenocorticotropin (ACTH) and beta-lipotropin (beta-LPH)/beta-endorphin (beta-EP) by the human medullary thyroid carcinoma (MTC). In a patient with MTC but without Cushing's syndrome, the response of plasma CT, ACTH and cortisol levels to a calcium infusion, lysine vasopressin (LVP) and dexamethasone were measured. A parallel increase of these hormones in response to calcium and LVP was seen, while there was a paradoxical increase of CT during dexamethasone infusion. Incubation of MTC fragments obtained at surgery showed a significant correlation of the secretion of CT, ACTH and beta-LPH/beta-EP in response to calcium, LVP and dexamethasone. The concomitant release of these hormones in vivo and in vitro could be compatible with the synthesis of a common precursor molecule for CT, ACTH and beta-LPH/beta-EP in MTC, although this was not substantiated by gel-chromatography of the tumor extract. Corticotropin releasing factor, a regulator of the normal processing of pro-opiococorticoid precursor molecule in the anterior pituitary gland, is also able to activate ACTH, beta-LPH/beta-EP and calcitonin secretion from the malignant C-cell of the thyroid. (Author abstract) (42 Refs)

3. IMMUNOREACTIVE ACTH IN NUDE MOUSE TUMORS DERIVED FROM HUMAN SMALL CELL CARCINOMA OF THE LUNG CELL LINES (MEETING ABSTRACT)

Cate CC, Pettengill OS, Sorenson GD
Dartmouth Medical School, Hanover, NH, 03755
Fed Proc; 41(3):333 1982

Ectopic ACTH production in nude mouse tumor xenografts derived from several continuous long term human small cell carcinoma of the lung (SCCL) cell lines was assayed and compared to levels produced by the cells in vitro. Inoculations of 9 different cell lines gave rise to tumors that repeatedly and predictably contained high, moderate, and low concentrations of immunoreactive ACTH. Relative iACTH concentrations in primary or serially passaged transplantable tumors were consistent with levels measured in culture media and cell extracts of the corresponding parent cell lines. Sephadex G-50 fine gel elution profiles of iACTH in culture media and cell or tumor extracts indicated that almost the entire ACTH content existed as relatively high molecular weight precursor forms with only very insignificant amounts eluting with trace-labeled synthetic human peptide. ACTH production by SCCL cell lines appears to be a relatively stable characteristic that persists in nude mouse xenograft models. (no Refs)

4. MECHANISM OF LONG-TERM CATECHOLAMINE DEFICIENCY IN RAT HYPOTHALAMUS AFTER IRRADIATION.

Bazanova NV, Prokudina EA
Central Res. Roentgeno-Radiological Inst., Leningrad, USSR
Radiobiologiia; 22(1):19-24 1982

The mechanism of radiation-induced catecholamine deficiency in the hypothalamus was studied in male rats irradiated with 400 rads. Animals were sacrificed 1, 3, 6, and 12 mo after irradiation, and the rate of catecholamine metabolism in the hypothalamus was determined. Progressive decrease of the concentration of dopamine and norepinephrine was associated with the deficiency of dihydroxyphenyl-alanine (DOPA). Administration of L-DOPA and monoamine oxidase inhibitor resulted in normalization of catecholamine metabolism. (9 Refs) (In RUS)

5. MULTIPLE CELL LINES FROM PATIENTS WITH MALIGNANT MELANOMA: MORPHOLOGY, KARYOLOGY, AND BIOCHEMICAL ANALYSIS.

Semple TU, Moore GE, Morgan RT, Woods LK, Quinn LA
Div. Surgical Oncology, Denver General Hosp., 750 Cherokee St., Denver, CO, 80204
JNCI; 68(3):365-380 1982

Of 23 cell lines representing eight patients with malignant melanoma, one cell line from each patient has been extensively characterized by means of phase morphology, ultrastructural morphology, biochemical markers, steroid receptor protein analysis, and steroid hormone production. Extensive cytogenetic characterization was compiled from seven of the eight cell lines. The melanocytic derivation of the tumor cell lines was supported by the detection of the catecholamines epinephrine, norepinephrine, and dopamine. In addition, well-defined melanosomes were present in six of the seven lines whose ultrastructures were examined morphologically. None of the lines produced alpha-fetoprotein, beta-human chorionic gonadotropin, or carcinoembryonic antigen in detectable amounts. The individuality of the cell lines was confirmed by phenotypic patterns of isozymes and by karyology. (Author abstract) (16 Refs)

6. ERYTHROPOIETIN FORMATION DURING HYPOXIA IN MICE WITH IMPAIRED RESPONSIVENESS TO ERYTHROPOIETIN INDUCED BY IRRADIATION OR 5-FLUOROURACIL INJECTION.

Barcelo AC, Bozzini CE
Catedra de Fisiologia, Facultad de Odontologia, M.T. de Alvear 2142, Buenos Aires 1122, Argentina
Experientia; 38(4):504-505 1982

Plasma erythropoietin levels during continuous exposure to hypobaric hypoxia in mice with marrow aplasia induced by whole body x-irradiation or 5-fluorouracil injection were higher than in control mice similarly exposed. These findings give support to the hypothesis that a relationship exists between erythropoietin production rate and erythroid responsiveness to the hormone. (Author abstract) (11 Refs)

7. GROWTH HORMONE RELEASING FACTOR IN A HUMAN TUMOR (MEETING ABSTRACT)

Cronin M, Rogol A, Login I, Keefer D, MacLeod R, Thorner M
University of Virginia Medical School, Charlottesville, VA, 22908
Fed Proc; 41(3):1488 1982

The release of a growth (GH) releasing factor (GRF) was indicated by the normalization of an acromegalic woman's serum GH after surgical removal of a pancreatic tumor. The medium into which the tumor was placed (RPMI-1640, HEPES, 10% horse and 2.5% fetal calf serum, antibiotics) was tested for GRF activity in primary cultures of male rat pituitary cells. GH secretion was stimulated at 5 min and 4 hours while there was no effect on prolactin release when a 1:10 dilution of the tumor medium (TM) and control medium (CM) was compared. Dilution beyond 1:30 reduced the GRF effect. A 1:3 TM dilution also stimulated release of newly synthesized 3H-GH about 2.5 fold from rat hemipituitaries at all times between 10 and 120 min of incubation. The tumor cells were dispersed and grown in vitro. Electron micrographs after 8 weeks reveal that many of the cells contain membrane-bound cytoplasmic granules of 150-225 nm with a dense core surrounded by an electron lucent halo. (no Refs)

8. PROLACTIN STORAGE IN A CLONAL STRAIN OF RAT PITUITARY TUMOR CELLS IS CELL-CYCLE DEPENDENT.

Kiino DR, Burger DE, Dannies PS
Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
J Cell Biol; 93(2):459-462 1982

GH4C1 cells (GH cells) are a clonal strain of rat pituitary tumor cells which secrete prolactin. We measured intracellular prolactin at different stages of the cell cycle using flow microfluorometry. Prolactin was stained by an indirect immunocytochemical technique using fluorescein isothiocyanate (FITC)-conjugated antiserum, and DNA was stained simultaneously with propidium iodide. We found that prolactin storage in GH cells was cell-cycle dependent; prolactin storage increased as cells passed from G1 to S to G2 + M. We have shown previously that insulin and 17beta-estradiol act synergistically to increase intracellular prolactin three- to sevenfold and slow the rate of cell growth to approx 70% of control cells. In this study we observed that insulin and estradiol increased prolactin storage at each stage of the cell cycle but did not affect the cell-cycle distribution of the population even though cell growth was slowed. We conclude that insulin and estradiol did not increase prolactin storage by affecting the cell-cycle distribution of the population. (Author abstract) (13 Refs)

9. INDUCTION OF PROLACTIN-DEFICIENT VARIANTS OF GH3 RAT PITUITARY TUMOR CELLS BY ETHYL METHANESULFONATE: REVERSION BY 5-AZACYTIDINE, A DNA METHYLATION INHIBITOR.

Ivarie RD, Morris JA

Dept. Molecular and Population Genetics, Univ. Georgia, Athens, GA, 30602

Proc Natl Acad Sci USA; 79(9):2967-2970 1982

GH3 cells are a rat pituitary tumor line expressing two pituitary peptide hormones, prolactin (rPRL) and growth hormone. Recently, it was found that the DNA alkylating agent ethyl methanesulfonate can induce the appearance of rPRL-deficient GH3 cell variants at a high frequency (ca 20-30%). As shown here, such variants cannot be induced at high frequency by irradiation of wild-type GH3 cells with ultraviolet light, indicating that the effect may be specific to treatment with alkylating agents. Furthermore, the DNA methylation inhibitor 5-azacytidine reverted an ethyl methanesulfonate-induced rPRL-deficient variant into rPRL-expressing cells at high frequency (ca 50%). The revertants were stable for at least 30-35 generations. These results support the hypothesis that the alkylating agent may promote the specific methylation of the rPRL gene or a gene regulating its activity, either one of which leads to inactivation of expression of the rPRL gene in GH3 cells. (Author abstract) (52 Refs)

10. ON THE MECHANISM OF 5-BROMODEOXYURIDINE INDUCTION OF PROLACTIN SYNTHESIS IN GH CELLS (MEETING ABSTRACT)

Hanes SD, Biswas DK

Department of Pharmacology, Harvard School of Dent Med, Boston, MA, 02115

Fed Proc; 41(3):1294 1982

Treatment of prolactin-nonproducing (PRL-) substrains of GH (growth hormone) (rat pituitary tumor) cells with 5'-bromodeoxyuridine (BrdUrd) induces prolactin (PRL) synthesis in these cells. Induction of PRL synthesis can be correlated with concomitant increased levels of cytoplasmic translatable and cDNAPRL hybridizable RNAPRL sequences. Analysis of nuclear RNAPRL sequences revealed several RNA species of approximately 25-30S, 18-19S and 12-13S. Only the 12-13S RNA species could be detected in the cytoplasmic poly(A) RNA fraction. Elevated levels of both nuclear and cytoplasmic RNAPRL sequences are observed after BrdUrd treatment of these GH cell substrains. These results suggest that BrdUrd induction of PRL synthesis in PRL-strains is mediated via transcriptional steps. The molecular mechanism/s involved in such stimulation of transcription in relation to the regulation of expression of specific genes in eukaryotic cells has been probed into and these results will be presented. (no Refs)

CLINICAL, DIAGNOSTIC AND PROGNOSTIC STUDIES

11. CARCINOID TUMORS OF THE ALIMENTARY TRACT.

Beaton HL
Mt. Sinai Sch. Medicine, New York, NY
CA; 32(2):92-99 1982

The chemical and pharmacologic nature of carcinoid tumors of the alimentary tract is discussed. Topics include history, clinical presentation, histology, malignant carcinoid syndrome, and treatment. Clinical presentation in 59 patients is described with regard to diagnosis, site of origin, and presence of nodal metastases. Five peptides may be secreted by functioning carcinoids: serotonin, 5-hydroxytryptophan, kallikrein, histamine, and ACTH. The term malignant carcinoid syndrome (MCS) applies to a group of symptoms affecting the vasomotor, gastrointestinal and cardiopulmonary systems. Cutaneous flushing, which occurs in 95% of patients with MCS, is probably due to a combination of humoral substances secreted by the tumor. Surgery is the primary treatment. The av time from onset to death from the disease is 8 yr. (34 Refs)

12. SEROTONIN IMMUNOREACTIVITY IN CARCINOID TUMOURS DEMONSTRATED BY A MONOCLONAL ANTIBODY.

Cuello AC, Wells C, Chaplin AJ, Milstein C
Univ. Dept. Pharmacology, South Parks Road, Oxford OX1 3QT, England
Lancet; 1(8275):771-773 1982

Formalin fixed, paraffin embedded carcinoid tumor samples which were up to 5 years old were specifically stained by the rat monoclonal antibody YC5/45 directed at serotonin immunoreactive sites. In addition, one malignant islet cell tumor associated with the carcinoid syndrome stained strongly with the antibody and one bronchial adenoma of carcinoid type was stained weakly. This commercially available monoclonal antibody could be widely used for the diagnosis of carcinoid tumors. (Author abstract) (15 Refs)

13. IN VITRO MONOCYTE MATURATION IN SQUAMOUS-CELL CARCINOMA OF THE LUNG: INFLUENCE OF HUMORAL FACTORS.

Dent RG, Cole PJ
Papworth Hosp., Papworth, Cambridgeshire, England
Br J Cancer; 45(4):522-530 1982

A previously described defect of in vitro monocyte maturation in patients with squamous-cell carcinoma of the lung (SCC) has been investigated further. The maturation of patients' monocytes in pooled normal human serum was significantly better than in autologous serum. Conversely, the maturation of normal control monocytes was significantly depressed in patients' serum. The defect has been shown to be due to the presence of an inhibitory factor, rather than the lack of a necessary component in the patients' serum. Artificially aggregated gamma-globulin inhibited monocyte maturation in vitro, but the presence of immune complexes in the serum of many patients with SCC did not correlate well with the depression of in vitro maturation of monocytes from the same patient. Similarly, pregnancy-associated alpha2-glycoprotein, in increased amounts in the serum of patients with SCC, showed no correlation with monocyte maturation. The addition of soluble extracts of tumor, but not of surrounding normal lung tissue significantly inhibited monocyte maturation. The results suggest that the defective monocyte maturation in patients with SCC is at least in part due to serum inhibitory factors, which are likely to be a heterogeneous group. (Author abstract) (34 Refs)

14. ACTH AND RELATED PEPTIDE HORMONES IN SERA AND TISSUES OF LUNG CANCER PATIENTS (MEETING ABSTRACT)

Luster W, Gropp C, Havemann K

Department of Hematology and Oncology, University of Marburg, Marburg, W. Germany

VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

ACTH, beta-endorphin, alpha-MSH (melanocyte stimulating hormone) and methionin enkephalin were determined by radioimmunoassay in the plasma of patients with lung cancer and in normal controls. ACTH was increased in 33% of patients with oat cell carcinoma and in 25% of patients with large cell carcinoma. Beta-endorphin and alpha-MSH levels were elevated in 45% respectively 53% of patients with oat cell carcinoma. In 12 patients with high beta-endorphin values beta-LPH was measured separately. In these patients beta-LPH levels mostly were higher than beta-endorphin levels. Serial determinations of ACTH and beta-endorphin showed a good correlation of the response to therapy. Beta-endorphin and beta-LPH like activity could be detected in chromatographic fractions of lung tumor extracts. ACTH, beta-endorphin, beta-LPH and alpha-MSH could also be demonstrated in paraffin sections of lung tumors using an immunoperoxidase method. (no Refs)

15. CALCITONIN AND ACTH IN PATIENTS WITH LEUKEMIA AND LYMPHOMA (MEETING ABSTRACT)

Pfluger KH, Gropp C, Havemann K

Abt Hamatologie/Onkologie, University of Marburg, Marburg, W. Germany

VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

Ectopic production of calcitonin (CT) and ACTH is frequently associated with human malignancy especially with bronchogenic carcinoma. About 50% of patients with acute leukemia exhibited markedly elevated CT serum levels, comparable to small cell carcinoma of the lung and in contrast to other solid tumors. Extremely high levels (greater than 1000 pg/ml) only occurred in patients with acute leukemia or blast crisis of CML. In these diseases CT seems to be a suitable marker for early diagnosis of relapse. In chronic leukemia, Morbus Hodgkin and Non-Hodgkin Lymphoma only slightly elevated CT levels in the range of 10% could be demonstrated. Since CT was present in different high molecular weight forms in serum and extracts of leukemic cells it is believed to be produced as a precursor by the malignant cells. In contrast, ACTH is only elevated in 5% of patients with hemoblastoses. Only in 3 cases of acute leukemia extremely high ACTH levels were found. In one instance the secretion of an autoantigenic high molecular weight precursor form of ACTH could be demonstrated. (no Refs)

16. PLATELET PARTICIPATION IN HEMOSTASIS DISTURBANCES IN PATIENTS WITH LYMPHOPROLIFERATIVE SYNDROMES.

Zawilska K, Komarnicki M, Psuja P, Sowier J, Wysocki K
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Pol Arch Med Wewn; 66(4):297-302 1981

Platelet count and platelet aggregation caused by adenosine diphosphate, collagen and epinephrine were studied in 32 untreated patients (22 men and 10 women, median age 37 yr) with Hodgkin's disease (HD) and in 50 patients (41 men and 9 women, median age 49 yr) with non-Hodgkin's lymphomas (NHL), and the results were correlated with the therapeutic results and grade of malignancy. The platelet counts were 153,000/cubic mm (mm3) in the patients with HD and 122,000/mm3 in those with NHL compared with a control value of 160,000/mm3 (p less than 0.01). The platelet counts were lowest in the NHL patients not responding to treatment and in those with NHL of low-grade malignancy. The platelet function showed no significant changes in the patients with HD compared with the controls, and there were no significant differences between patients with high-grade and low-grade malignancy of HD, nor between responders and nonresponders. Among the NHL patients, the disturbances in the platelet function were most pronounced among those with NHL of high-grade malignancy and the nonresponders. (14 Refs) (In POL)

17. PATHOGENESIS OF GESTATIONAL TROPHOBLASTIC NEOPLASMS.

Berkowitz RS, Goldstein DP
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Pathobiol Annu; 11:391-411 1981

Epidemiology, presenting signs and symptoms, and natural history of molar pregnancy (MP), locally invasive trophoblastic disease (TD), metastatic TD, clinicopathological correlations, and the role of human chorionic gonadotropin (HCHG) in TD are discussed. The reported incidence of MP significantly varies in different regions of the world. The frequency of hydatidiform mole (HM) in Asian nations is 7-10x greater than the reported incidence in North America or Europe. Presenting signs and symptoms of the first 306 patients with MP who were treated at the New England Trophoblastic Disease Center are summarized. HM are well recognized to have a potential for local invasion and distant metastasis. Consecutive molar gestations in the same individual have been reported. Recurrent MP was associated with worsening trophoblastic histology and increased incidence of proliferative trophoblastic complications in the successive episodes of HM. HM may be categorized as either a classic or partial mole based on gross morphology, histopathology, and karyotype. Classic moles have generalized hydatidiform swelling of the villi and no associated embryonic or fetal tissues. Locally invasive trophoblastic tumors (TT) occur in approx 15% of patients after molar evacuation and less frequently following other pregnancies. Trophoblastic tissue metastasizes in approx 5% of patients after molar evacuation and infrequently following other gestational events. Patients with a marked cellular reaction to their TT had a greater opportunity for prolonged survival. All patients with TT have elevated HCHG that are proportional to the number of viable tumor cells. (50 Refs)

18. ECTOPIC HUMAN CHORIONIC GONADOTROPIN PRODUCTION IN DIFFERENT FORMS OF MALIGNANCY.

Das S, Bhattacharyya S, Chowdhury JR
Chittaranjan Natl. Cancer Res. Center, 37 S.P Mookherjee Road, Calcutta 700026, India

Indian J Med Res; 74:904-906 1981

Human chorionic gonadotropin (hCG) has been determined by specific radioimmunoassay in the sera of subjects bearing a variety of malignant and nonmalignant lesions. The placental hormone was detected in 59% of the malignant conditions the highest percentage of detectability being 65% in cancer of cervix, followed by 44.8% in breast cancer. (Author abstract) (7 Refs)

19. THE ROLE OF HUMAN CHORIONIC GONADOTROPIN IN SEMINOMATOUS TESTICULAR TUMOR.

Masuda M
Dept. Urology, Sch. Medicine, Kobe Univ., Japan

Hinyokika Kiyo; 28(1):1-12 1982

In order to investigate the significance of human chorionic gonadotropin (hCG) in seminoma of the testis, serum hCG levels in peripheral and testicular venous bloods before orchiectomy and hCG levels in tumor tissues were measured in 25 cases. Additionally, tissue specimens of seminomas were immunohistochemically studied for the cellular location of hCG by peroxidase antiperoxidase (PAP) method. The results were as follows: The rates of elevation of serum hCG levels were 47.8% in peripheral venous blood, and 88.8% in testicular venous blood. HCG levels in tumor tissues were detected in all cases, and their average level was 437.6 ng/g tissue. In case hCG levels in tumor tissues were less than 150 ng/g tissue, serum hCG were negative both in testicular and peripheral venous bloods. However, in case showing the level more than 150 ng/g tissue, serum hCG in testicular venous blood were positive, and if more than 200 ng/g tissue, serum hCG in peripheral venous blood were positive in all cases. By PAP method, hCG was demonstrated within syncytiotrophoblastic giant cell (STGC) in 10 of 22 cases, and in 2 cases of 10, cellular localizations of hCG were found not only in STGC but also in tumor cells of seminoma. In the positive group by PAP method, both serum hCG levels and rates of elevation of serum hCG levels in peripheral and testicular venous bloods were higher than the negative group. And the same result was obtained in hCG levels in tumor tissues. It was concluded that the measurement of serum hCG levels in peripheral venous blood before orchiectomy is useful as a serum marker for seminoma. STGC were mostly seen by PAP method in the cases which showed high hCG levels before orchiectomy among the cases diagnosed as pure seminoma histopathologically by hematoxylin-eosin stained specimens. Those should be regarded as non-seminomatous germ cell tumors. (Author abstract) (40 Refs) (In JPN)

20. ENDOCRINOLOGICAL STUDIES ON PROSTATIC CARCINOMA. 1. PLASMA HORMONE PROFILES IN PATIENTS WITH PROSTATIC CARCINOMA.

Morioka M
Dept. Urology, Okayama Univ. Medical Sch., Okayama, Japan

Nippon Hinyokika Gakkai Zasshi; 72(8):953-966 1981

Levels of plasma testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), cortisol, luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin were determined in 47 patients (49-87 yr old) with prostatic carcinoma before and during antiandrogen therapy. Hormonal dynamics were not related to the course of the disease. Rather, the levels of the hormones were primarily a result of pharmacological effects of the drugs. However, pretreatment levels of DHEA-S were significantly lower in the 26 Stage IV carcinoma patients than in the Stage I, II, and III patients; this was thought to be related to aging factors and the general condition of the patients. Synthetic progestogens (50-100 mg/day, 3-79 mo) and diethylstilbestrol diphosphate (DES-DP; 300 mg/day, 3-18 mo) decreased T-cell production and levels of DHEA and DHEA-S while estramustine phosphate (EP; 560-840 mg/day, 4-22 mo) inhibited T-cell production but had no inhibitory effect on DHEA or DHEA-S. The EP more strongly inhibited FSH levels than synthetic progestogens. Based on ACTH-Z and single dose metyrapone tests in patients undergoing treatment, DES-DP was thought to have inhibitory effects on DHEA and DHEA-S due to mild inhibition of ACTH and C17-C20 lyase activity in the adrenal glands. On the other hand, the EP was thought to have no inhibitory effect on steroid production in the adrenal glands. No relationship was found between adrenal androgen levels and the reactivation of prostatic carcinoma in patients who relapsed. (46 Refs) (In JPN)

21. TRANSSPHENOIDAL MICROSURGICAL REMOVAL OF GROWTH HORMONE-SECRETING PITUITARY ADENOMAS.

Baskin DS, Boggan JE, Wilson CB
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J Neurosurg; 56(5):634-641 1982

A series of 137 patients with growth hormone (GH)-secreting pituitary adenomas were treated by transsphenoidal surgery during a 10-year period. Group A comprised patients for whom this surgery was the first therapeutic intervention, and Group B included those who underwent the surgery after previous therapeutic intervention. The results were analyzed considering preoperative and postoperative endocrinological, neurological, ophthalmological, and neuroradiological data. Remission was defined as clinical response and a normal postoperative GH level, and partial remission as clinical response and postoperative reduction of the GH level by more than 50%. Any other result was considered failure. The mean follow-up period was 37.1 months; follow-up review was achieved in all the patients. Among the 120 patients in Group A, remission was achieved in 80 (78%) patients with transsphenoidal surgery alone, and in an additional 16 (16%) after postoperative irradiation (combined response rate, 94%). All failures and patients with partial remission had preoperative GH levels of more than 50 ng/ml and suprasellar extension of the tumor. There were no deaths; 8% of patients had minor surgical morbidity; 5% had new hypopituitarism postoperatively. Of patients subsequently irradiated, 71% developed hypopituitarism. Among the 35 patients in Group B, remission was achieved in 26 (74%), partial remission was obtained in 2 (6%), and 7 (20%) were considered treatment failures. There were no deaths, and the morbidity rate was 14%; 66% of patients had hypopituitarism postoperatively. Of the eight patients who had received prior irradiation only, seven (88%) went into remission. All failures and partial responders had preoperative GH levels greater than 40 ng/ml; 56% had suprasellar extension. These results confirm the efficacy of the transsphenoidal approach for the treatment of GH-secreting pituitary adenomas. (Author abstract) (49 Refs)

22. GLYCOPROTEIN HORMONE ALPHA-SUBUNIT SECRETION IN PATIENTS WITH PITUITARY ADENOMAS: INFLUENCE OF TRH, LRH AND BROMOCRIPTINE.

MacFarlane IA, Beardwell CG, Shalet SM, Ainslie G, Rankin E
Dept. Endocrinology, Christie Hosp., Manchester, England
Acta Endocrinol (Copenh); 99(4):487-492 1982

Twelve patients with pituitary adenomas and increased serum concentration of the glycoprotein hormone alpha-subunit were studied. Eight patients were acromegalic and one had a FSH producing tumor. The adenomas in 9 patients had undergone subtotal operative removal and/or external irradiation but no patient was studied within 3 mo of these treatments. Many of the acromegalic patients, with moderately elevated alpha-levels, showed marked increases in alpha-concentration after TRH and/or LRH, compared with controls. The non-acromegalic patients, with the highest alpha-levels, showed poor responses to releasing hormones. These results suggest that excessive alpha-subunit secretion in acromegalic patients is often under hypothalamic control whereas in non-acromegalic patients it is often autonomous. Seven patients, 4 with acromegaly, were then given oral bromocriptine, 5 mg over 3 hr. There was significant fall in log mean alpha-level at 4 and 5 hr (p less than 0.02). Six patients took bromocriptine for 1-2 mo. Log mean alpha-concentration was significantly reduced at the end of treatment (p less than 0.02) and then recovered to basal levels after stopping treatment for one wk. Alpha-subunit hypersecretion in some patients with pituitary adenomas is therefore modulated by dopaminergic control mechanisms. (Author abstract) (12 Refs)

23. HYPOGONADISM IN MALE PATIENTS WITH METASTATIC CANCER PRIOR TO CHEMOTHERAPY.

Chlebowski RT, Heber D
Div. Medical Oncology, Harbor-Univ. California Los Angeles Medical Center, 1000 West Carson St., Torrance, CA, 90509
Cancer Res; 42(6):2495-2498 1982

Gonadal hormonal function was assessed in 44 adult males with disseminated cancer prior to chemotherapeutic treatment of their cancer by determination of plasma testosterone, free testosterone, and luteinizing hormone (LH) levels. Low values for both testosterone (43% decreased) and free testosterone (66% decreased) were seen in this largely malnourished cancer population, in which 82% of patients were less than 90% of ideal body weight. Four patterns of serum testosterone and LH were seen: (a) normal testosterone and normal LH (12 cases); (b) normal testosterone and high LH (13 cases), consistent with early primary hypogonadism; (c) low testosterone and high LH (10 cases), consistent with frank primary hypogonadism; (d) low testosterone and normal or low LH (9 cases), consistent with secondary hypogonadism. Significantly decreased ideal body weight was found in the group with low testosterone and low or normal LH level. We conclude that decreased gonadal hormone secretion is frequently seen in adult males with advanced cancer and malnutrition even prior to chemotherapy treatment. (Author abstract) (34 Refs)

24. GONADAL FUNCTION AFTER PLATINUM, VINBLASTINE, BLEOMYCIN (PVB) +/- ADRIAMYCIN (A) IN TESTICULAR CANCER (MEETING ABSTRACT)

Drasga RE, Williams SD, Stevens EE, Patel DN, Einhorn LH, Rohn RJ
Indiana University Hospital, Indianapolis, IN, 46223
Proc Am Soc Clin Oncol; 1:C-407 1982

Patients with disseminated testicular cancer and no prior retroperitoneal lymphadenectomy treated with PVB +/- A were evaluated with sperm counts, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone. Since 1979, 37 men have been prospectively studied. Median followup is 18 months. Before treatment, 20 of 27 were oligospermic and only 3 could meet requirements for sperm banking. FSH was elevated in 1 of 37. After two months, 17 of 18 were aspermic, 18 (100%) were oligospermic, and FSH was elevated in 16 of 29. After 1 year, 7 of 8 remain aspermic and 12 of 13 have elevated FSH. Also, 19 patients treated between 1975-1979 were retrospectively evaluated. Median followup from the start of therapy was 36 months. Normal sperm counts were found in 8 of 16. FSH was normal in 10 of 18. LH was normal in 12 of 18. Testosterone was normal in 14 of 18. Five of 17 have impregnated their wives resulting in 3 healthy babies, 1 ongoing pregnancy, and 1 spontaneous abortion. These results show that: (1) Significant impairment of spermatogenesis exists before therapy precluding the possibility of sperm banking in most patients, (2) Cisplatin-based combination chemotherapy has substantial effects on gonadal function, and (3) A high degree of recovery of spermatogenesis occurs sometime after 2 to 3 years from the initiation of treatment. (no Refs)

25. CHEMOTHERAPY OF MALIGNANT MELANOMA.

Thiers BH
Dept. Dermatology, Medical Univ. South Carolina, Charleston, SC
J Am Acad Dermatol; 6(3):412-415 1982

No consistently effective chemotherapy employing standard agents has yet been developed for any stage of malignant melanoma (MM). Steroid hormone binding activity has been identified in a small percentage of MMs, but even these patients seem unlikely to respond to hormonal therapy. New approaches to the chemotherapy of MM include the use of melanotropin (MSH) or conjugates of MSH with antitumor agents (eg, daunomycin) and treatments based upon the series of enzymatic reactions responsible for melanin formation. Until a safe, effective chemotherapy is discovered, early diagnosis and adequate surgical treatment will give the MM patient the best chance for a long-term remission. (50 Refs)

26. PROLACTIN UPDATE.

Mehta AE, Tolis G, Goodyer C, McInnes R
Div. Reproductive Endocrinology, Royal Victoria Hosp., Montreal, Quebec H3A 1A1, Canada
Pathobiol Annu; 11:337-389 1981

Structure, chemistry, measurements of prolactin (PRL), PRL circulating forms, PRL in body tissues and fluids, sites of origin of PRL, role of PRL, control of PRL secretion, effects of nonreproductive and reproductive hormones and glands and of nonendocrine disease states on PRL, abnormalities of PRL secretion, diagnostic tests, and prolactinomas are discussed. Pituitary tumors secreting excessive amounts of PRL can be treated surgically, medically, or with radiotherapy. Effects of pregnancy on the PRL-producing adenoma are discussed. (269 Refs)

27. THE MANAGEMENT OF PROLACTIN-SECRETING PITUITARY TUMORS.

George SR, Burrow GN
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J Endocrinol Invest; 4(4):459-467 1981

Over 40% of pituitary tumors secrete prolactin. Presumptive diagnosis is based on exclusion of other causes of hyperprolactinemia, the presence of hypothyroidism, chronic renal failure, stalk section, hypothalamic space-occupying or infiltrative lesions, and neuroradiological demonstration of a pituitary fossa abnormality. Treatment may be surgical, radiologic, or chemotherapeutic, or a combination of these. The transsphenoidal approach is the surgical approach of choice. Indications for surgical treatment and evaluation of results are discussed. Years may be necessary for effects of radiation treatment to become apparent. Medical treatment may be with dopamine agonists. Bromocriptine is effective for treatment of hyperprolactinemic amenorrhea, galactorrhea and the associated hypogonadism. An approach to patients with prolactin-secreting adenomas is proposed. Proper therapy requires information about the size of the tumor, associated symptoms and signs, and the desires of the patient regarding fertility. Bromocriptine is being used more often in both patients with microadenomas and those with macroadenomas. Bromocriptine may also be useful in improving resectability of tumors preoperatively. (71 Refs)

28. ELECTRON MICROSCOPIC STUDY OF HUMAN PROLACTIN PRODUCING PITUITARY ADENOMA.

Shimizu T, Kimura R, Tamura M, Takeda F
Dept. Neurosurgery, Gunma Univ., Maebashi 371, Japan
Neurol Med Chir (Tokyo); 21(12):1219-1228 1981

An electron microscopic study of 15 cases (14 female, 1 male) of prolactin-producing pituitary adenomas was performed. All of the female patients manifested galactorrhea. Nine patients harbored intrasellar microadenoma, and the others harbored large tumor masses showing suprasellar extension. The age distribution was from 20 to 70 yr, with an av of 25.7 yr for the microadenoma-group and an av of 42.7 yr for the large tumor-group. Electron microscopic observations of adenomas obtained from 11 patients who had not received bromocriptine revealed adenoma tissue composed of polyhedral adenoma cells. The findings suggest an increased cellular activity of the adenoma cells in hormone synthesis and release. No difference in the fine structures was noticed between the microadenomas and large tumors. Bromocriptine was given preoperatively in three cases, and the serum prolactin levels were markedly reduced. In two cases, the secretory granules were increased in number and accumulated within the cytoplasm. In the other case the secretory granules decreased in number and frequently were hardly observed. The findings in bromocriptine-treated cases suggest that the drug acted to reduce the cellular activity in both hormone synthesis and release. The remaining case clinically showed the galactorrhea-amenorrhea syndrome, but an electron microscopic study disclosed a fine structure similar to that of the non-functioning adenoma. The ultrastructural findings in this particular case suggest an interference in production, release and transport of FIF by suprasellar extension of the adenoma. Electron microscopy is an essential tool in establishing the final diagnosis of prolactin-producing adenomas of the pituitary. (31 Refs) (In JPN)

29. THE IMPACT OF SURGICAL TREATMENT ON ENDOCRINOLOGICAL STATUS OF PITUITARY ADENOMAS ASSOCIATED WITH HYPERPROLACTINEMIA.

Sato O, Hotta H, Nakagawa T, Sohma F, Hasunuma M, Tsuchida H, Tanabe S, Koybayashi K, Inoue Y

Dept. Neurosurgery, Sapporo Medical Coll., Sapporo, Japan

No Shinkei Geka; 10(1):55-62 1982

The authors investigated the surgical impact on the endocrinological status of pituitary adenomas associated with hyperprolactinemia. Thirty-nine pituitary adenomas were classified as 18 PRL-secreting macroadenomas, 16 PRL-secreting microadenomas and 5 non-secreting hypothalamus-invading hypothalamic adenomas. The surgical removal of adenomas was performed through the transsphenoidal approach in 31 cases, through the transfrontal approach in 6 cases and through the combined transsphenoidal-transfrontal approach in 2 cases. The pre- and postoperative endocrinological status was examined on both serum basal levels and hormonal reserves of PRL, HGH, TSH, LH, FSH, ACTH and cortisol and the serum basal levels of estradiol, progesterone and testosterone were also examined. The surgical impact on the basal serum hormonal levels and reserves other than of PRL showed no statistical difference between transsphenoidal and transfrontal approach and the transfrontal surgery was considered not to be a more hazardous procedure. The severe damage to the function of the pituitary posterior lobe was not found after surgery. (12 Refs) (In JPN)

30. TRANSSPHENOIDAL REMOVAL OF PITUITARY TUMORS: EXPERIENCE WITH 167 PATIENTS.

Tucker HS, Grubb SR, Wigand JP, Taylon A, Lankford HV, Blackard WG, Corales RL, Becker DP

Box 111, Medical Coll. Virginia Station, Richmond, VA, 23298

Va Med; 109(3):164-170 1982

Experience with transsphenoidal removal of pituitary tumors in 67 patients is reported. The operative approach used was that of Hardy, employing an operating microscope. Intraoperative fluoroscopic monitoring was used in cases with macroadenomas with significant extension. Wide bony exposure of the floor of the sella turcica was important. Complete inspection of the sella contents was conducted prior to removal of microadenomas. For larger adenomas with significant suprasellar extension, removal was facilitated by using a sustained Valsalva maneuver. Of 67 women with prolactin-secreting tumors, 44 were cured and 1 developed hypopituitarism (HOP). Of 40 patients with growth hormone-secreting tumors and acromegaly, 30 were cured and 4 developed HOP. Of 12 with Cushing's disease, 10 were cured and 1 died from surgery. Of six patients with Nelson's syndrome, four were cured. No cure was observed in the one patient with a thyroid-stimulatng hormone secreting tumor. Of 41 patients with large nonsecreting tumors or prolactin-secreting tumors, 20 were cured , 1 developed HOP, and 1 died from surgery. (14 Refs)

31. IMMUNOREACTIVE PROLACTIN IN EPITHELIAL CELLS OF NORMAL AND CANCEROUS HUMAN BREAST AND PROSTATE DETECTED BY THE UNLABELED ANTIBODY PEROXIDASE-ANTIPEROXIDASE METHOD.

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Dept. Pathology, Sch. Medicine, Univ. Maryland, Baltimore, MD, 21201

Cancer Res; 42(6):2317-2324 1982

A rabbit antiserum to ovine prolactin was used with the peroxidase-antiperoxidase method to search for immunoreactive prolactin in normal and pathological human breast and prostate. The immunostaining of pituitary cells appeared specific for prolactin since both ovine and human prolactin abolished immunostaining when they were added to the anti-prolactin serum. We stained sections of normal breast and normal prostate. Results suggested that the immunostaining of normal breast and prostate was related to the presence of immunoreactive prolactin in epithelial cells of these organs. In prostate, immunostaining was confined to the secretory cell population. In breast, immunostaining seemed to occur throughout the breast parenchyma. The immunostaining of normal breast epithelium was markedly heterogeneous. This was less pronounced in normal prostate epithelium. Sixty-four percent of the primary prostate adenocarcinomas which were examined showed strong staining reactions with anti-prolactin serum. Two of three metastatic tumors of prostate origin had similar strong staining reactions. Infiltrating duct carcinomas of the breast were strongly stained with anti-prolactin serum, but most breast fibroadenomas were not stained. None of seven adenocarcinomas of the colon tested as controls were stained by anti-prolactin serum. The results suggested that the immunostaining of breast and prostate carcinomas was related to immunoreactive prolactin. The results reported here emphasize the value of the peroxidase-antiperoxidase method in the study of hormone target organ interactions as well as in retrospective studies of pathological materials. (33 Refs)

32. EFFECTS OF BROMOCRIPTINE ON CSF PROTEINS AND AMINES IN PATIENTS WITH EMPTY SELLA SYNDROME, ACROMEGALY AND PROLACTIN PRODUCING PITUITARY ADENOMAS.

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J Endocrinol Invest; 4(4):393-397 1981

The effect of bromocriptine (BR) on cerebrospinal fluid (CSF) proteins and amines was studied in seven patients with hypersecretion of prolactin (PRL) and/or growth hormone due to empty sella syndrome (4 patients) and pituitary adenomas (3). Over a period of 4-6 wk, oral doses of BR were gradually increased from 1.25 mg/day. Using mass fragmentography, the CSF metabolites, 5-hydroxyindoleacetic acid (5-HIAA), homovanillinic acid (HVA) and 4-hydroxy-3-methoxyphenylglycol (HMPG) were determined. Proteins in CSF and serum were studied by isoelectric focusing. Changes consistent with blood-CSF barrier disturbances were found in five patients. Most abnormal protein isoelectric focusing patterns were found in the pH region of transferrin components and asioalotransferrin. The drug apparently affects the transferrin microheterogeneity but does not alter S-transferrin levels. BR therapy also caused depression of the dopamine metabolite HVA, noradrenalin, adrenalin and 5-HIAA. HMPG remained unchanged. Thus, besides affecting amine and trace metal metabolism, BR also affects protein metabolism. (19 Refs)

33. TRANSPLANTATION HYPERPARATHYROIDISM: TUMORLIKE GROWTH AND AUTONOMOUS FUNCTION OF AUTOGRAFTS OF THE HYPERPLASTIC PARATHYROID.

Klempa I, Rottger P, Schneider M, Frei U, Koch KM
Zentrum der Chirurgie, Johann-Wolfgang-Goethe-Universitat, Theodor-Stern-Kai 7, D-6000 Frankfurt a. M. 70, W. Germany
Langenbecks Arch Chir; 356(3):191-204 1982

Forty-one patients with secondary uremic hyperparathyroidism resulting from chronic renal failure were treated by total parathyroidectomy followed by autotransplantation of parathyroid tissue into the musculature of the forearm. Parathormone levels were measured in blood drawn from the cubital vein of the transplant-bearing arm and the contralateral arm initially at 3-mo intervals and later at 6-mo intervals. Observation time was 5 yr. Transplant tumors developed in five patients within 7-33 mo of transplantation. Locally continuous and discontinuous invasion of surrounding tissue, blood vessels, and musculature by hyperplastic parathyroid tissue was found. Microscopic examination showed an increase in mitoses in hyperplastic tissue compared with normal tissue, indicating malignant character of the hyperplastic tissue. DNA histograms showed peaks for normal and hyperplastic parathyroid tissue at the diploid level. The hyperplastic tissue, however, showed a shift towards the tetraploid level. Histograms of less nodular tumors showed distinct peaks at both diploid and tetraploid levels, while in histograms of nodular tumors these peaks were less distinct. Two patients showed normal DNA values in excised parathyroid tissue but elevated levels in transplant tissue; two patients showed elevated levels in both the excised tissue and the transplanted tissue. Occurrence of hyperplasia in transplants indicates that the procedure is not justified in treatment of renal osteodystrophy. (28 Refs) (In GER)

34. DEFERRED PARATHYROID AUTOGRAFTS WITH CRYOPRESERVED TISSUE AFTER REOPERATIVE PARATHYROID SURGERY.

Saxe AW, Spiegel AM, Marx SJ, Brennan MF
(c/o Brennan) Dept. Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Arch Surg; 117(5):538-543 1982

Between August 1975 and March 1981, 12 patients underwent forearm parathyroid autotransplantation with cryopreserved tissue following reoperative parathyroid surgery. Tissue had been cryopreserved 2 to 18 mo. Follow-up ranged from 4 to 66 mo (median, 18 mo) following autotransplantation. All patients required calcium supplementation as a condition for autografting; six patients were no longer receiving calcium supplementation at most recent follow-up and in one patient the dosage was being tapered. The presence of a parathyroid hormone gradient of 2:1 or greater correlated well with freedom from calcium supplementation. Of seven patients with preautograft and postautograft urinary cyclic adenosine monophosphate (cAMP) determinations, three with increases following transplantation did not require calcium, three without increases continued to require calcium, and the patient whose dosage was being tapered had increased urinary cAMP levels. (Author abstract) (33 Refs)

35. COMPUTED TOMOGRAPHY (CT) AND THE LOCALISATION OF PARATHYROID TUMOURS (MEETING ABSTRACT)

Adams JE, Adams PH, Mamtora H, Isherwood R
Department of Diagnostic Radiology, University of Manchester, Manchester, England
Ann R Coll Surg Engl; 63(6):440 1981

Several methods have been devised for the preoperative localization of parathyroid adenoma. The combination of selective arteriography and venous sampling for serum parathyroid hormone levels will localize the tumors preopertively in 90% of patients. This technique is invasive, time-consuming, and potentially hazardous, and even with this procedure some tumors still elude localization. Computed tomography (CT) provides a noninvasive technique for demonstrating the anatomy of the neck and mediastinum. To assess its value in the preoperative localization of parathyroid tumors 18 patients with primary hyperparathyroidism were scanned. The probable site of parathyroid tumor was reported from the CT scans by two independent radiologists. In addition observations were made on scan quality, anatomical detail, and the presence of thyroid abnormality. The CT predictions of the two observers were compared and related to the operative findings. The role of CT in the localization of parathyroid tumors was discussed. (no Refs)

36. LYMPHOCYTE RESPONSIVENESS TO THYMOSIN IN ANGIOIMMUNOBLASTIC LYMPHADENOPATHY WITH LYMPHOMATOUS TRANSFORMATION.

Taylor SG
Rush-Presbyterian-St. Luke's Medical Center, 1725 W. Harrison St., Chicago, IL, 60612
Med Pediatr Oncol; 10(2):171-174 1982

Lymphocytes from a patient with angioimmunoblastic lymphadenopathy with lymphomatous degeneration were tested in vitro for thymosin responsiveness. The percentage of lymphocytes forming spontaneous (E) rosettes to sheep red blood cells (SRBC) was 37 and 32% in the absence of thymosin on two separate occasions. Lymphocytes incubated with thymosin formed rosettes in 55 and 43% when incubated with 0.1 ug/ml and 66 and 63% when incubated with 100 ug/ml, respectively. The patient subsequently received thymosin while in a preterminal condition. No clinical response to thymosin was apparent and lymphocytes tested 8 days after starting thymosin treatment demonstrated reduced thymosin responsiveness (31% without thymosin vs 37% with 100 ug/ml). The failure to respond clinically to thymosin treatment may be related to the preterminal condition. The in vitro responsiveness to thymosin suggests that thymosin effect should be examined earlier in the course of this disease process. (Author abstract) (12 Refs)

37. THYROGLOBULIN IMMUNOHISTOCHEMISTRY: NEW ASPECTS OF PATHOPHYSIOLOGY AND DIFFERENTIAL DIAGNOSIS OF BENIGN AND MALIGNANT GOITER.

Dralle H, Bocker W
Zentrum Chirurgie, Klinik fur Abdominal- und Transplantationschirurgie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover 61, W. Germany
Langenbecks Arch Chir; 356(3):205-212 1982

Aspects of thyroglobulin immunohistochemistry (TGIHC) are described. TGIHC uses tissue samples fixed in formalin and imbedded in paraffin and is capable of demonstrating the functional status of benign and malignant thyroid alterations. TGIHC allows differentiation of goiters and thyroid adenomas and metastases of thyroid or other adenocarcinomas and provides information for planning of radioiodine therapy (RIT) and control of therapy. Examination of tissues indicates that nontoxic goiter develops by thyroid stimulating hormone (TSH)-dependent conversion of active thyroid follicles into inactive follicles. Inactive follicles become aggregated to form macrofollicles. Active follicles may become independent of TSH, becoming autonomous. The final stages of nontoxic goiter are probably irreversible. Thyroid adenomas include 'hot' and 'cold' nodes. Hot, endocrinologically active nodes include autonomous adenomas. Cold nodes include other main cell adenomas and differentiated adenomas, such as oxyphilic and clear-cell adenomas. In examining metastases positive TGIHC indicates that the primary tumor is a thyroid carcinoma; negative results indicate a primary adenocarcinoma of some other origin. The intensity of thyroglobulin synthesis (TGS), as indicated by TGIHC, facilitates planning of RIT, since TGS correlates with uptake of radioiodine. (16 Refs) (In GER)

38. DIRECT DETERMINATION OF FREE THYROXINE IN TWO SIMULTANEOUS RADIOIMMUNOASSAYS WITH DIFFERENT TEST PRINCIPLES: VALIDITY OF TEST RESULTS DERIVED FROM AN AREA OF MARKED IODINE DEFICIENCY.

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Allgemeines Krankenhaus Bamberg, Untere Sandstrasse 32, D-8600 Bamberg, W. Germany
Nuklearmedizin; 21(1):30-35 1982

The serum concentration of protein-binding factor 4 (FT4) was measured in euthyroid patients with and without malignant or nonmalignant goiter, patients on thyroxine substitution therapy (TST), patients on oral contraceptives (OC), and patients with subclinical hyperthyroidism, using FT4 test kits from Amersham-Buchler (AB) and Corning Medical (CM). Results with both kits correlated well with thyroid functional status, except in patients receiving OC. The CM kit produced a wider scattering of values then did the AB kit. Use of commercial FT4 kits requires further evaluation. (23 Refs) (In GER)

39. FAMILIAL INAPPROPRIATE TSH SECRETION: EVIDENCE SUGGESTING A DISSOCIATED PITUITARY RESISTANCE TO T3 AND T4.

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Section d'Endocrinologie, Institut de Pathologie, C.H.U. B23, B4000 Sart Tilman, Liege 1, Belgium
J Fadocrinol Invest; 4(4):413-422 1981

The pituitary-thyroid relationships of a 40-yr-old euthyroid woman with recurrent goiter, constant hyperthyrotropinemia and high thyroid hormone levels were studied. Following administration of triiodothyronine (T3) and thyroxine (T4), clinical results suggested that thyroid hormone resistance predominated at the pituitary level for T4. No evidence of a pituitary adenoma or other thyroid stimulating hormone secreting tumor was found. A study of the patient's family indicated a familial distribution with autosomal dominant transmission. (54 Refs)

40. VARIATIONS OF THYROID HORMONES IN SERUM DURING 5-FU TREATMENT (MEETING ABSTRACT)

Breier S, Karner M, Guinzburg R, Rozenfeld L
Jewish Hospital of Buenos Aires, Buenos Aires, Argentina
Proc Am Soc Clin Oncol; 1:C-120 1982

Because of the frequency of hyperthyroid symptoms in patients under 5FU (5-fluorouracil) treatment, we studied humoral hormonal changes in a group of patients. We assayed in 17 patients with different types of tumors (colon, rectal, breast, bladder), Triiodothyronine Thyroxine, TSH (thyroid stimulating hormone) and TRH (thyrotropin-releasing hormone)-TSH stimulation test, previous therapy. The patients underwent the schedule with 5FU 650 mg/m2, IV, each 3 days during 4 weeks. In 15th day of treatment and 4th week after interrupting 5FU, hormonal assays were repeated (T3, T4, TSH). We observed in 41% of cases that thyroxine values increased above the normal range. Though T3 also increased comparatively to basal values, only in 11% of the cases it increased abnormally. The percentage of increases of T4 was 57.5% and of T3, 35.7%. Clinical symptoms were in accord to humoral fluctuations. When interrupted 5FU, hyper functioning symptoms disappeared and humoral hormonal values returned to normal. We suggest that those observed changes may be due to an effect of 5FU. (no Refs)

41. RADIOIODINE THERAPY OF FOLLICULAR THYROID CARCINOMA.

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Praxis; 71(13):562-566 1982

Radioiodine therapy (RIT) of follicular thyroid carcinoma is described. The aim of RIT is elimination of tumor cells that accumulate iodine. Accumulation of radioiodine in histologically confirmed thyroid carcinoma and in some cases in metastases is an indication for RIT. Thyroid carcinomas are relatively radioresistant, requiring dose of 30,000-40,000 rad. The high radiation dose requires removal of normal thyroid tissue. Uptake of 131I by tumor cells can be stimulated by endogenous or exogenous thyroid stimulating hormone (TSH). Exogenous TSH carries the risk of allergic reaction. TSH can also block hypothalamic-hypophyseal regulation. The effective half-life of radioiodine can be extended by suppression of TSH-stimulation, achieved by substitution therapy with L-triiodothyronine. Administration of 1.8 ug/kg in fractioned doses is well tolerated. Extending the half-life of radioiodine carries the risk of damaging the bone marrow. This risk can be minimized by administration of inactive iodine. Computer tomography allows precise estimation of tumor mass, a critical factor in response to therapy. RIT produces tumor regression in approx 33% of patients with bone metastases. RIT produces complete elimination of tumor in 50% of patients with pulmonary metastases, regression in 33%, and temporary arrest of growth in the remainder. The most effective treatment of follicular thyroid carcinoma requires close cooperation of all involved medical disciplines. (6 Refs) (In GER)

42. THYROID CARCINOMA: CLINICAL DISCUSSION OF 35 CASES.

Wang PW, Huang MJ, Huang BY, Huang HS, Chen MF, Wang CS, Chou FF
Dept. Internal Medicine and Surgery, Chang Gung Memorial Hosp., Taipei, Taiwan
Taiwan I Hsueh Hui Tsa Chih; 80(12):1349-1356 1981

Incidence, clinicopathologic findings and therapy are described for 35 patients (12 males, 23 females; 6-77 yr old) with pathologically verified thyroid carcinoma. Diagnosis indicated 21 papillary carcinoma, 4 follicular carcinoma, 6 anaplastic carcinoma, 3 medullary carcinoma and 1 case of fibrosarcoma. Papillary carcinoma occurred in all age groups while anaplastic carcinoma occurred mainly in older patients (49-71 yr old) with 82% over 60 yr old. The growth of papillary carcinoma was slow while that of anaplastic carcinoma was fast, with the growth of follicular and medullary carcinomas intermediate. Cervical lymphatic metastasis occurred in about 50% of patients with papillary or follicular carcinoma, in 1/3 of those with anaplastic carcinoma and in 2/3 of those with medullary carcinoma. Local invasion occurred in all patients with anaplastic carcinoma but in less than 1/3 of patients with the other types. Distant metastasis was most frequent in follicular carcinoma but least frequent in papillary carcinoma. During a 3-yr follow-up period, the most effective surgical treatment was found to be subtotal thyroidectomy; external radiotherapy, iodine-131 radiotherapy and long-term thyroid hormone therapy were also helpful. (19 Refs) (In CHI)

43. THE IMPORTANCE OF EARLY DIAGNOSIS IN PATIENTS WITH HEREDITARY MEDULLARY THYROID CARCINOMA.

Wells SA, Baylin SB, Leight GS, Dale JK, Dilley WG, Farndon JR
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Ann Surg; 195(5):595-599 1982

Ninety-two patients from 12 kindreds with hereditary medullary thyroid carcinoma (MTC) were evaluated. We sought to determine if the stimulated plasma calcitonin (CT) level at the time of diagnosis was of prognostic significance. The patients were divided into four groups according to their preoperative stimulated plasma CT levels (1) 250-1,000 pg/ml (n = 25); (2) 1,000-5,000 pg/ml (n = 36); (3) 5,000-10,000 pg/ml (n = 8); (4) greater than 10,000 pg/ml (n = 23). Compared between the four groups were several parameters, including incidence of regional lymph node metastases, incidence of residual MTC postthyroidectomy (as indicated by increased (greater than 300 pg/ml) plasma CT levels after operation), incidence of distant metastases, and incidence of death. Also compared were the incidences of microscopic or gross MTC in thyroidectomy specimens. The incidence of regional lymph node involvement ranged from a minimum of one (4%) of 25 patients in Group 1 to 13 (57%) of 23 patients in Group 4. Similarly, plasma CT levels were elevated in only one (4%) of 25 patients in Group 1 compared to 14 (61%) of 23 patients in Group 4. There was no evidence of distant metastases or death in the patients in Groups 1, 2, or 3. In the 23 patients in Group 4, however, four (17.4%) had distant metastases and two (8.7%) died of disease during the period of observation. Of the 25 patients in Group 1, MTC was evident only by microscopic examination in 14 (56%). Eleven (44%) of the patients in Group 1 had macroscopically evident medullary thyroid carcinoma. This is in contrast with patients in Group 4 where all 23 had grossly evident MTC. These data indicate that the stimulated plasma CT level at the time of diagnosis is an excellent prognostic indicator of the extent of a disease in patients with hereditary MTC. Aggressive screening of kindred members at risk of critical importance for establishing the diagnosis and instituting therapy at a time when the neoplasm is confined to the thyroid gland. (Author abstract) (8 Refs)

44. HYPOTHYROIDISM AND WOUND HEALING. OCCURRENCE AFTER HEAD AND NECK RADIATION AND SURGERY.

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Arch Otolaryngol; 108(5):289-291 1982

A retrospective 5-yr review of patients treated for cancer of the larynx disclosed a high prevalence of hypothyroidism after combined therapy. A total of 29 patients were studied. Seven (24%) of the 29 patients had hypothyroidism develop in the posttreatment period (0 to 2 yr). Two (22%) of the 9 patients treated with surgery alone and 5 (25%) of 20 patients treated with a combination of surgery and radiation had hypothyroidism develop. An additional 10 patients treated with radiation alone remained clinically euthyroid, and no thyroid function tests were performed. Of the five patients who became hypothyroid after treatment with a combination of surgery and radiation, two had fistulae develop that were resistant to intensive local care. They closed promptly after treatment of the hypothyroidism. Of the two patients who had hypothyroidism develop after surgery alone, one had fistulae develop that were resistant to local care, but responsive to thyroid hormone. These patients should have thyroid function tests done in the early postoperative period, and those found to be hypothyroid should be treated promptly. (Author abstract) (13 Refs)

45. CANCER OF THE ENDOCRINE SYSTEM.

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Dept. Surgery, Memorial Sloan-Kettering Cancer Center, Cornell Univ., New York, NY
Cancer - Principles and Practice of Oncology. DeVita VT, Hellman S, and Rosenberg SA, ed. Philadelphia, Lippincott, 1926 pp., 1982.

Cancer of the thyroid gland, adrenal gland, and endocrine pancreas, carcinoid tumors, and multiple endocrine neoplasia syndrome are reviewed. Topics discussed with respect to thyroid gland cancer include history, epidemiology, anatomic considerations, pathology (follicular, medullary, undifferentiated carcinomas), natural history of thyroid carcinomas, pathogenesis (radiation-induced), patterns of spread, clinical presentation, diagnostic methods, standard work-up, treatment (surgery, radioactive iodine), results, complications of treatment, and follow-up. Adrenal gland neoplasms are considered with regard to anatomic considerations, the adrenal cortex, natural history of adrenal cortical tumors, clinical presentation, methods of diagnosis and staging of functional tumors, results of localization studies, adrenal medulla, natural history of pheochromocytoma, treatment of metastatic disease, and results of treatment. The epidemiology, natural history, clinical presentation, and diagnosis of tumors of the endocrine pancreas are discussed. Also examined are the anatomy of the pancreas, Zollinger-Ellison syndrome (surgical treatment and results), insulinoma, glucagonoma, WDHA syndrome (watery diarrhea, hypokalemia, and achlorhydria syndrome), somatostatinoma, pancreatic polypeptide, surgical management of pancreatic endocrine tumors, and treatment of metastatic disease. The history, epidemiology, genetics, pathology, pathogenesis, diagnosis, treatment, results, and screening of carcinoid tumors are discussed. The history, epidemiology, natural history, clinical presentation, treatment, and results in multiple endocrine neoplasia are considered. (474 Refs)

46. COMPUTED TOMOGRAPHY STUDY OF 100 CASES OF ADRENAL GLAND DISORDERS.

Picard JD, Lacrosniere L, Bard DM, Ducellier R, Gruson B, Lubrano JM, Luton JP, Parienty R, Perez R, Pradel J, Wellers M
Scanner-Intercliniques Hartmann, Neuilly-sur-Seine, France
Bull Acad Natl Med (Paris); 165(1):57-73 1981

Computed tomography (CT) findings are presented for 100 patients with adrenal gland disorders, including 75 with adrenal hormone hypersecretion (30 pheochromocytomas, 8 Conn's adenomas, 34 metabolic hypercorticism, and 4 multi-secretory tumors), 19 with non-secreting tumors (7 primary and 12 secondary), 3 with adrenal hematomas, and 3 with adrenal insufficiency. CT diagnoses of adrenal tumors and pseudotumors were based on augmentation of one or both of the adrenal glands, homogeneity or heterogeneity of adrenals, and relationship to neighboring organs. Pheochromocytomas (PT) were characterized by regular contours and, in half of the cases, homogeneity. Of non-homogenous PT forms, 2/3 showed areas of necrosis. Of the 30 PT, 4 were malignant. CT is useful in the diagnosis of PT: false negatives are rare and false positives exceptional. Indications for CT in the diagnosis of metabolic hypercorticism include the determination of the etiology of Cushing's disease and the detection of primary or recurrent adrenal tumors. CT is of little use in defining adrenal hyperplasia related to Cushing's disease. In the cases of primary adrenal tumors, CT allows the determination of tumor location within the adrenal gland, of its relationship to neighboring organs, and of the existence of hepatic metastases. Adrenal metastases are usually bilateral and often discovered by chance. (11 Refs) (In FRE)

47. DIAGNOSTIC AND INTERVENTIONAL ANGIOGRAPHY IN ACUTE GASTROINTESTINAL HEMORRHAGE.

Rahn NH, Tishler JM, Han SY, Russinovich NA
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Radiology; 143(2):361-366 1982

The use of vasopressin infusion or arterial embolization in the treatment of 87 patients with gastrointestinal hemorrhage is reviewed. A bleeding point was identified angiographically in 46 patients (53%), with a higher success rate in those with upper gastrointestinal hemorrhage (63%) than in those with lower (39%) gastrointestinal hemorrhage. Vasopressin infusion in 33 patients completely stopped hemorrhage in 14 and slowed hemorrhage pending surgery in another 5. Gelfoam embolization was successful as definitive therapy in 12 of 15 patients. Mortality as a result of hemorrhage or its sequelae was 40% in patients with upper gastrointestinal hemorrhage and 21% in those with lower gastrointestinal hemorrhage. (Author abstract) (22 Refs)

EFFECTS ON NORMAL AND NEOPLASTIC CELLS AND TISSUES

48. HORMONE-DEPENDENT TERMINAL DIFFERENTIATION IN VITRO OF CHICKEN ERYTHROLEUKEMIA CELLS TRANSFORMED BY TS MUTANTS OF AVIAN ERYTHROBLASTOSIS VIRUS.

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Cell; 28(4):907-919 1982

Chicken erythroblast cell strains and a cell line transformed by ts mutants of avian erythroblastosis virus (AEV) terminally differentiate when shifted to the nonpermissive temperature (42 C). The differentiated cells resemble mature erythrocytes with respect to morphology and ultrastructure, expression of differentiation-specific cell-surface antigens, pattern of protein synthesis and hemoglobin content. Terminal differentiation is dependent on conditions favoring the differentiation of normal erythroid progenitor cells, including an erythropoietin-like factor. Colonies of ts AEV cells grown at 42 C in semisolid medium resemble erythrocyte colonies derived from normal erythroid progenitor cells. The colonies obtained were comparable in size or slightly larger than the late erythroid precursor (CFU-E) colonies. These results suggest that AEV-transformed cells are blocked at a stage of differentiation that is more advanced than that of the uninfected target cells. ts AEV cells are irreversibly committed to terminal differentiation within 20 to 30 hr after shift to 42 C. (Author abstract) (42 Refs)

49. EPINEPHRINE-INDUCED CHANGES IN THE CYCLIC NUCLEOTIDE CONTENT OF FISH MELANOMA CELLS.

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Dept. Biology, Keio Univ., Yokohama 223, Japan
Gen Comp Endocrinol; 47(1):88-93 1982

Intracellular levels of adenosine 3',5'-monophosphate (cyclic AMP) and guanosine 3',5'-monophosphate (cyclic GMP) in melanoma tissues developed in platyfish and swordtail hybrids were determined by radioimmunoassay. The melanoma tissues were composed mostly of pigment cells, many of which responded to epinephrine with pigment aggregation. The aggregated melanosomes redispersed gradually by washing the cells with physiological saline, and rapidly by the perfusion with theophylline. Determination of intracellular levels of cyclic nucleotides revealed that epinephrine produced a small but significant decrease in cyclic AMP level, whereas theophylline elicited a remarkable increase in the intracellular concentration of cyclic AMP. On the other hand, the change in the levels of cyclic GMP was not significant among the tissues subjected to the different experimental conditions. The present results suggest that the centrifugal and centripetal translocations of melanosomes within melanophores are regulated directly by the intracellular concentration of cyclic AMP. (Author abstract) (37 Refs)

50. PROPERTIES AND CHARACTERISTICS OF ADENYLATE CYCLASE IN NORMAL AND FIBROCYSTIC BREAST EPITHELIAL CELLS IN HUMANS (MEETING ABSTRACT)

Foecking MK, Abou-Issa H, Minton JP
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Fed Proc; 41(3):1409 1982

Basal, fluoride and hormone-stimulated activities of adenylate cyclase (AC) have been studied in mammary epithelial cells of human tissues freed from adipose tissue. Epithelial cells were isolated by collagenase treatment of normal and fibrocystic breast tissues. The apparent Km for MgATP2-in both tissues is 1.0x10(-4) M. AC in both tissues is stimulated only by catecholamines and prostaglandins (PGE1, PGE2). The enzyme was maximally activated (2 x basal activity) by L-epinephrine (EPI) with an apparent Km of 2.0 x 10(-6) M. Norepinephrine also stimulated the activity but with an increased apparent Km of 8 x 10(-5) M. PGE1 and PGE2 (at 10(-6) M) stimulated the basal activity of AC by 140% and 95% respectively. EPI and PGE1 together have no additive stimulatory effect indicating separate receptor sites for each hormone. The stimulation by EPI or PGE1 is potentiated 4-and 2.5-fold respectively by the addition of 10 x 10(-5) M Gpp (NH)p. The apparent Km for Gpp(NH)p is approximately 15 uM. The catecholamine stimulation appears to be mediated through Beta 2 adreno-receptors. AC from fibrocystic breast has an increased responsiveness to EPI compared to normal tissue both in the absence and presence of Gpp(NH)p. However no difference was observed in PGE1-responsiveness in both tissues. The results suggest increased catecholamine responsiveness play a developmental role in fibrocystic breast disease. (no Refs)

51. GONADOTROPIN-RELEASING HORMONE ANALOGUES FOR PROSTATE CANCER: UNTOWARD SIDE EFFECTS OF HIGH-DOSE REGIMENS ACQUIRE A THERAPEUTICAL DIMENSION.

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Eur Urol; 8(3):129-134 1982

Gonadotropin-releasing hormone (Gn-RH), a hypothalamic decapeptide, mediates the synthesis and release of pituitary luteinizing hormone (LH). Synthetic Gn-RH analogues with prolonged duration of action are therapeutically administered with 'pro-fertility' intention to overcome endogenous Gn-RH deficiency, ie hypogonadotropic hypogonadism and related disorders. When Gn-RH analogues are chronically administered in high supraphysiological dosages, however, a paradoxical effect of pituitary overstimulation becomes evident: gonadotropin release is reduced, Leydig cell responsiveness is impaired, and testosterone secretion is blocked to castrate levels. Metabolic mechanisms involved include desensitization of the pituitary to Gn-RH, down-regulation of Gn-RH receptors, the depletion of the releasable LH pool, the breakdown of physiological feedback mechanisms, as well as direct interactions of the Gn-RH analogue with the Leydig cell. It is tempting to assume that, on the basis of this untoward side effect, high dose Gn-RH analogues will acquire a therapeutical dimension in the palliative treatment of prostate cancer. The therapeutical effect of castrate levels of testosterone is achieved without orchiectomy, cardiovascular side effects of estrogens are avoided, and the drug is conveniently applicable via the pernasal route. From the data available today Gn-RH analogues in overstimulatory dosage can be expected to be safe and effective in the palliative treatment of prostate cancer and would thus prove a true alternative to conventional contrasexual measures. (Author abstract) (35 Refs)

52. REGULATION OF INTRACELLULAR PROTEIN DEGRADATION BY INSULIN AND GROWTH FACTOR.

Ballard FJ, Nield MK, Francis GL, Knowles SE
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Acta Biol Med Ger; 40(10/11):1293-1300 1981

Some of the properties of growth factor (GF) action on protein breakdown (PBD) in cultured cells are described. Insulin, epidermal GF (EGF), fibroblast GF (FGF), insulin-like GF 1 (IGF-1), insulin-like GF 2 (IGF-2), and fetal calf serum (FCS) were tested for inhibitory effects on PBD in 19 cell lines. Examples of cells which are sensitive to other GF are presented. PBD in all cells tested was inhibited by FCS, IGF-1, and IGF-2. GF produce a stimulation of DNA synthesis. The addition of IGF-1 to HTC hepatoma cells showed that withdrawal of GF is accompanied by a rapid change to the higher rate of PBD. Marked inhibitions of PBD were observed in HTC hepatoma cells with insulin, IGF-1, and FCS but when these GF are added to the cells at concentrations known to give maximal effects, no additivity was observed. Concentration effects of GF in IMR90 fibroblasts, HTC, and MH1C1 hepatoma cells are presented. When effects of both insulin and IGF are considered together, PBD is reduced selectively in transformed cells. PBD is much more effectively inhibited by insulin, EGF, IGF-1, IGF-2, or FCS in the mid-passage than in the senescent cells. The poorer response does not appear to reflect an already low rate of autophagic proteolysis in the aged cells because inhibition of lysosomal proteolysis by ammonia gives an equal response in both mid-passage and aged cells. PBD is inhibited by 0.5% colostrum to approx the same extent as found with 10% FCS in six lines and only slighty less in MCF7 and OS104 cells. In both the H35 hepatoma and Swiss 3T3 mouse fibroblasts, 0.5% colostrum is more effective than 10% FCS. (9 Refs)

53. KININ METABOLITES: A NEW PRINCIPLE IN THE REGULATION OF LOCAL INFLAMMATORY HOST DEFENSE BY INVADING TUMOURS (MEETING ABSTRACT)

Stahl KW, Roch-Arveiller M, Giroud JP, Mathe G
Department de Pharmacologie, Hospital P Brousse, F-94800 Villejuif, France
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

Local antiinflammation which helps invasively growing tissues (malignant tumors, attaching trophoblast) to overcome host defense is likely not be an independent phenomenon but a secondary, reactive process responding to primary inflammation elicited by cell destruction. On the basis of such an obviously physiological and simple concept, apparently conflicting reports on antagonistic modulations of tumor development by inflammatory processes and our findings concerning the (bio)chemical characterization of antikinin may find some straightforward explanation. Recently, we have shown that kinin metabolites mimic the described inhibitory effect of the antikinin peptide fraction on peritoneal macrophages as B1-receptor agonists. Literature reports on kinin metabolizing enzyme (EC 3,4,12,3) activity found with the chemotactic factor inactivator (CFI) isolated from transplantation tumors and of a high kinin(ogen) content in malignant lung tumors from humans are highlighted in view of the emerging hypothesis of antikinin being a so far unindentified kinin metabolite. This may provide some clue to the mechanism of inflammatory feedback control in invading tissue and is actually under further investigation. (no Refs)

54. PREVENTION OF TRANSPLACENTAL CARCINOGENESIS BY THE IMMUNOLOGIC HORMONE LYMPHOTOXIN (MEETING ABSTRACT)

Ransom JH, Evans CH, DiPaolo JA
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Fed Proc; 41(3):379 1982

Development of interventive measures to control cancer would be facilitated by monitoring carcinogenesis in vivo with an in vitro assay of morphologic transformation. Syrian hamsters at the 10-11th day of gestation were injected ip with 3 mg diethylnitrosamine (DEN)/100 g. Two days later, fetuses were excised, the fetal cells dissociated and 2000 cells seeded/60 mm dish for colony formation. The frequency of morphologically transformed colonies was determined after 7 days. The mean transformation frequency per cell seeded was 1 x 10(-4) with a 3.6% efficiency of colony formation. Ip injection of an immunologic hormone preparation reduced the transformation frequency by 46%. The preparation was the diafiltered and concentrated lymphokines of phytohemagglutinin stimulated hamster peritoneal leukocytes. It contained 10,000 units of lymphotoxin but no detectable interferon. When DEN exposed cells were x-irradiated with 250 R in vitro and 9000 cells seeded/dish, an increased mean transformation frequency, corrected for x-ray toxicity, of 8.5 x 10(-4) per cell seeded was observed. The DEN + x-ray cocarcinogenic frequency of transformation was reduced 64% by ip injection of the immunologic hormone. This study indicates that immunologic hormones (eg lymphotoxin) can prevent carcinogenesis in vivo and that the in vitro quantitation of transformation provides a means for assessing passively administered and autochthonous effector mechanisms which control carcinogenesis in vivo. (no Refs)

55. MODULATION OF CELL COMPETENCE FOR INDUCTION OF DIFFERENTIATION IN MYELOID LEUKEMIC CELLS.

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Dept. Genetics, Weizmann Inst. Sciences, Rehovot 76100, Israel
J Cell Physiol; 111(1):9-14 1982

Physiological ways of modulating cell competence for induction of differentiation by a variety of compounds were investigated. Cell competence for induction of some differentiation-associated properties in differentiation-defective clones of mouse myeloid leukemic cells (MGI 7-1D 7-1) could be modulated for some inducers [macrophage-granulocyte inducing protein (MGI-2), lipopolysaccharide (LPS), and dexamethasone (DEX)] by the type of serum in the medium and for another inducer (insulin) by removing serum from the medium. The molecular of MGI that induced this differentiation was MGI-2. All MGI 7-1D 7-1 clones could be modulated for inducibility by MGI-2, LPS, and DEX, but only some of these clones could be modulated for inducibility by insulin. These modulations allowed induction of some but not all differentiation-associated properties, so that both procedures modulated in MGI 7-1D 7-1 clones the expression of some but not all the genes in the developmental program. (33 Refs)

56. ROLE OF NATURAL PROSTAGLANDINS IN THE CONTROL OF MURINE MAMMARY TUMOR VIRUS EXPRESSION.

Svec J, Svec P, Halcak L, Thurzo V
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J Cancer Res Clin Oncol; 103(1):55-67 1982

The regulation of murine mammary tumor virus (MuMTV) production by mammotropic hormones, hormonomimetic substances, and cyclic nucleotides was investigated. The virus produced in control and treated mammary tumor cell cultures was quantitated by measuring the supernatant reverse transcriptase activity in exogenous reaction using poly(rC).oligo(dG) as template-primer. Two days after exposure, the synthetic glucocorticoid, dexamethasone (DXMT), increased spontaneous MuMTV production at optimal concentration (0.1 umol) up to 10x. Dibutyryl derivative of cyclic AMP had no effect on spontaneous MuMTV production, whereas the drug potentiated suboptimal concentrations of the glucocorticoid. Natural prostaglandins, potent agonists of adenylate cyclase catalyzing intracellular synthesis of cyclic AMP, enhanced both basal (up to 5x) and DXMT-stimulated (up to 1.6 times) MuMTV replication. The MuMTV-stimulating activity of prostaglandins decreased in the order of PGA1 greater than PGE1 greater than PGB1 greater than PGF2 alpha. Prostaglandins can be replaced partially by norepinephrine and isoproterenol by enhancing the DXMT-mediated MuMTV stimulation, whereas these drugs remained without effect on spontaneous MuMTV production. Theophylline, an antagonist of cAMP-phosphodiesterase converting cAMP to AMP, enhanced the virus-stimulating activity of DXMT as well as of prostaglandins. The enhancement of MuMTV production by adenylate cyclase agonists do not correlate absolutely with the estimates of intracellular cAMP levels, since the highest amounts of cAMP have been repeatedly observed in cells treated with PGE1 and norepinephrine. The results indicate that besides hormones, other hormone-like substances and cyclic nucleotides may be involved in the complex mechanism of hormone-regulated MuMTV genome expression. (Author abstract) (55 Refs)

57. COMPARISON OF ACETYLATION OF NUCLEAR PROTEINS IN THE LIVER AND THYMUS OF RATS DURING IRRADIATION AND PROTECTION WITH SEROTONIN.

Babeniuk IuD, Blium IaB, Tsudzevich BA, Kucherenko NE
Faculty Biology, T. G. Shevchenko State Univ., Kiev, USSR
Radiobiologiia; 22(1):13-18 1982

Effect of serotonin (ST) on acetylation and radiosensitivity of nuclear proteins was studied in random-bred albino rats irradiated with 0.2 Ci/kg. ST (20 mg/kg, ip) was injected 15 min prior to irradiation. Irradiation increased the rate of acetylation of histone H1 in the liver and decreased the rate of acetylation of histone H1 in the thymus. ST produced similar changes in the rate of histone H1 acetylation. (18 Refs) (In RUS)

58. CELLULAR HETEROCHRONY AND NEOPLASIA.

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Med Hypotheses; 8(3):231-235 1982

The concept that 'timing changes' in gene regulation are responsible for malignant transformation and subsequent tumorigenesis is presented. Cells of regenerating rat liver 'retrodifferentiate' (RDF), taking on 'juvenile' or embryonic patterns of antigenic and genetic behavior. RDF is followed by a process of redifferentiation to normal tissue type. Primary malignant cells have often been compared to the invading cells of the trophoblast. Trophoblastic tissue and malignant cells have a number of similarities including their ability to move (metastasize), destroy their host's cells in advance of the invading cells, create a life support system by means of angiogenesis, and subvert their host's immune surveillance and monocyte-macrophage systems. Cellular heterochrony of RDF could explain these similarities. Attempts were made to relate human breast cancer and urogenital cancer to thyroid gland malfunction by showing a higher incidence of cancer in hypothyroidism and a lower incidence in euthyroid and hyperthyroid states. The hormones which render amphibians both neotenic and metamorphic are also possibly responsible for triggering timing changes in the tissues and cells of other metazoans. The observations that the thyroid hormones thyroxine (T4) and triiodothyronine (T3) enhance rat liver regeneration provide indirect evidence to support this hypothesis. T4 or T3 may act as an anticarcinogen. The use of a polar solvent can induce maturation changes in rhabdomyosarcoma transplantable tumor cells from mice and human colon cancer cells causing the cells to lose a marked degree of malignancy. The cancer cells appear to have metamorphosed and thus relinquished their juvenile or heterochronic behavior. (22 Refs)

59. HUMAN PROLACTIN AND HUMAN GROWTH HORMONE ALTER CELL SHAPE AND PROLIFERATIVE RATE OF HUMAN BREAST CANCER CELLS IN CULTURE (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:933 1982

The role of prolactin and growth hormone in the etiology of human breast cancer is unclear. Therefore, the biological effects of these hormones on a human breast cancer cell line, T47D, were examined. T47D cells contain a high concentration of receptor sites that bind human prolactin(hPRL) and human growth hormone(hGH). When T47D cells were maintained on plastic substratum, they grew as a 'cobblestone' monolayer and assumed a flat, polygonal snape. However, when cultured in the presence of hPRL or hGH(10 ng/ml to 1 ug/ml), and 1 ug/ml each of hydrocortisone(H), insulin(I), and triiodothyronine(T3), T47D cells became round; the cells were loosely attached to the plastic substratum and they aggregated into large clusters. Such changes were not observed if only hPRL or hGH were present, or if only HIT3 were present, indicating that hPRL and hGH require the synergism of the other three hormones(HIT3) to induce the shape change in T47D cells. Another lactogenic hormone, ovine prolactin, produced a similar effect as hPRL and hGH, whereas non-lactogenic hormones such as ovine growth hormone and human luteinizing hormone had no effect on the T47D cells. As well as having an altered shape, T47D cells proliferated twice as fast in serum-free medium supplemented with HIT3 only; T47D cells failed to proliferate in serum-free medium not supplemented with hormones. (1 Ref)

60. TRI-IODOTHYRONINE (T(3)) STIMULATES THE GROWTH OF MORRIS HEPATOMA CELLS GROWN IN CULTURE.

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Biochem Biophys Res Commun; 105(4):1611-1617 1982

Cell cultures from transplanted Morris Hepatoma number 44 and host liver from female Buffalo rats were grown in medium containing 10% fetal calf serum (FCS) depleted of iodothyronines. The growth of liver cells was reduced by a max of 20% under such conditions, while that of the hepatoma cells was inhibited approx 40%. Addition of 200 nanoM tri-iodothyronine (T3) to the medium restored growth rate to control levels in both liver and tumor cells. Addition of 200 nanoM T3 to control medium (total concentration of T3 400 nanoM), did not significantly augment the rate of liver or tumor cell replication. Differences in cell growth rate between iodothyronine depleted and control media were significantly different after 120 hr for liver and 24 hr for tumor cells. Thymidine kinase (TK) activity paralleled cell replication rate. A consistent and significant difference in TK activity compared to control values was observed only in cells grown in depleted medium after 48 hr of incubation. TK activity of hepatoma cells exceeded values of liver cells by a factor of 30-50 in all experiments. TK activity was markedly stimulated in cells grown in depleted medium supplemented with 200 nanoM T3 and control medium supplemented with 200 nanoM T3 compared to cells grown in control medium. Corresponding rates of hepatoma cell replication in such media did not significantly exceed those of cells grown in control media. Thus, T3 exerts a direct effect on the in vitro growth of hepatoma cells. Application of this method for studying the effect of hormones on receptor concentration and DNA and protein synthesis of neoplastic and normal tissue is suggested. (18 Refs)

61. CHARACTERIZATION OF HYPOTHALAMIC ORIGIN GROWTH FACTOR(S) FOR RAT PITUITARY TUMOR CELLS IN CULTURE (MEETING ABSTRACT)

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Fed Proc; 41(3):489 1982

Several hypothalamic hormones have been characterized which are delivered via the portal circulation to the anterior pituitary regulating pituitary hormone production. One of these hormones, TRH (thyrotropin-releasing hormone), has been implicated in the growth response of normal and neoplastic pituitary cells. To further explore the hypothalamus for additional activities that may participate in the regulation of pituitary growth, we have utilized a subclone (GH3/C14) of the original GH3 cell line as a sensor system for probing hypothalamic extracts. Although these cells cannot be used to study all of the physiological functions of the normal pituitary, they do respond to physiological concentrations of estrogens, glucocorticoids, thyroid hormones and TRH in a qualitatively similar manner to cultures of normal cells. Studies with extracts of various separated areas of the rat brain showed that hypothalamic extracts caused a sustained increase in cell number when added to serum-free medium, whereas cerebellum, cerebrum and brain stem extracts were inactive. The rat hypothalamic activity is stable in 1% acetic acid, and at neutral PH has an apparent molecular weight of 25,000 daltons. Large scale purification appears possible using an acid extract of ovine hypothalamus and modified assay procedure requiring only 10 hours, exposure to growth factor. (no Refs)

62. INCREASED SURVIVAL OF TUMOR-BEARING MICE AFTER ADMINISTRATION OF THYMOSIN PREINCUBATED SYNGENEIC BONE MARROW CELLS (MEETING ABSTRACT)

Cupissol D, Goldstein AL, Serrou B
Centre Paul Lamarque, Montpellier Cedex 34 033, France
Proc Am Assoc Cancer Res; 23:1017 1982

The present results are based on a system directly applicable to man, consisting of bone marrow transplants in C57Bl/6 mice with either methylcholanthrene induced tumor or Lewis tumor. Animals were treated by injection of syngeneic bone marrow cells from non-tumor-bearing mice. If these cells are preincubated in thymosin fraction 5 or alpha 1 before injection there is a significant retardation of tumor growth and metastatic disease followed by significantly increased survival time. In addition, we found that this action: 1) was T lymphocyte dependent and did not occur if bone marrow preincubated with thymosin was treated with anti-thy 1-2 serum; 2) was independent of NK activity. Mice treated with radioactive strontium showed no change for thymosin anti-tumor effects. Tumor bearing mice treated with CDDP (Cis-Platinum) or tumor local radiotherapy (16 grays) associated to thymosin preincubated bone marrow cells also demonstrated a significantly increased survival time as compared to mice treated by chemotherapy or radiotherapy alone. These results are sufficiently encouraging to warrant a randomized trial in order to evaluate the efficacy of administration of autologous bone marrow cells pretreated with thymosin after aggressive chemotherapy in the advanced solid tumor patient. (no Refs)

63. RESISTANCE TO L1210 MOUSE LEUKEMIA CELLS IN MODERATELY PROTEIN MALNOURISHED BALB/C MICE TREATED IN VIVO WITH THYMOSIN FRACTION (MEETING ABSTRACT)

Ronald V, Watson R, Petro TM

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Fed Proc; 41(3):357 1982

Female weanling BALB/c mice were fed a 20% casein control (C) or 4% casein low protein (LP) diet. The LP diet or treatment with bovine, a series of injections with thymosin fraction V (BTF5) totalling 700 ug, independently rendered mice more resistant to intraperitoneal (IP) growth of 10(7) L1210 mouse leukemia cell growth. In mice fed LP, reduced growth of the leukemia L1210 was correlated with increased mitogenic responsiveness of spleen lymphocytes to phytohemagglutinin (PHA) and increased levels of serum corticosterone. The growth in vitro of L1210 cells was significantly inhibited by corticosterone. Treatment of mice fed LP with BTF5 increased the resistance to L1210 cell growth above that in mice fed LP and injected IP with saline. For 7 days after the last BTF5 treatment mice fed LP had reduced serum corticosterone levels. However, these levels were still higher than those of mice fed C diet. The increased resistance to leukemia cell growth in mice fed LP treated with BTF5 was correlated with increased splenic lymphocyte responsiveness to PHA and an increase in development of cell mediated cytotoxicity 14 days after leukemia cell challenge. These data suggest that the increased resistance of moderately protein malnourished mice against cancer cell growth may be partially the result of increased in vivo corticosterone levels. (no Refs)

64. EFFECTS OF COMBINED THYMOSIN AND CYCLOPHOSPHAMIDE TREATMENT ON SYNGENEIC TUMOR GROWTH AND HOST SURVIVAL IN BALB/C MICE (MEETING ABSTRACT)

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Fed Proc; 41(3):407 1982

MOPC-315 tumor cells (10(6)) were inoculated subcutaneously into syngeneic BALB/c mice. After the tumor was palpable at day 9, a single dose of 20 mg/kg cyclophosphamide was given ip. One week later, the mice received thymosin fraction Fr 5 or alpha 1 7 times during 2 weeks in an effort to retard regrowth of tumor and enhance long-term survival. Injection of thymosin Fr 5 in microgram doses or thymosin alpha 1 in nanogram doses resulted in long-term survival of BALB/c mice. Thus, 80-100% of mice survived following thymosin Fr 5 or alpha 1 treatment, whereas 0-40% of control mice treated only with cyclophosphamide survived. The dose of thymosin Fr 5 and thymosin alpha 1, as well as the dose of cyclophosphamide, was critical in preventing reappearance of the tumor. Those animals which rejected the tumor following thymosin and cyclophosphamide treatment were completely resistant to a second challenge with the same dose of tumor cells. The experimental syngeneic tumor model used in this study was designed to correspond as closely as possible to clinical conditions. The results of this study indicate that thymosin is effective in reducing tumor growth and in prolonging survival in some syngeneic tumor-bearing mice in conjunction with chemotherapy. (no Refs)

65. DIFFERENTIATION OF K-562 CELLS: INDUCTION BY THYMOSIN FRACTION 5 (MEETING ABSTRACT)

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Fed Proc; 41(3):795 1982

K-562 cells differentiate along the erythrocytic, granulocytic, and monocytic series; hence K-562 cells are considered to be multipotential leukemic cells. These cells express both specific leukemia associated antigens (LAA) and Fc receptors. We initiated a study employing monoclonal antibody preparations to determine the presence of other surface membrane antigens on the K-562 cells. When evaluated with the Cytofluorograf for the binding of F(ab')2 fragment of goat anti-mouse IgG, K-562 cells from 6 or 7 day-old cultures did not bind anti-HLA-A,B,C, anti-HLA-DR, OKT10 (reactive with thymocytes, BM terminal transferase positive cells, BM precursor B cells, and myeloblasts), OKT11 (reactive with large thymic blasts), or anti-monocyte antibody. Over 90% of the cells bound the five monoclonal anti-K-562 antibody preparations of differing specificities. The incubation of cells with thymosin fraction 5 for 24 hours led to changes in the expression of some surface antigens. The number of HLA-A,B,C expressing cells was increased but the number of OKT10 binding cells was only noticeably increased. There was also an increased intensity of the expression of LAA. The fact that the incubation of the K-562 cells with thymosin fraction 5 resulted in the expression of HLA-A,B,C suggests that these cells could be induced to differentiate along the lymphocytic series. (no Refs)

66. RESISTANCE TO L1210 MOUSE LEUKEMIA CELLS IN MODERATELY PROTEIN-MALNOURISHED BALB/C MICE TREATED IN VIVO WITH THYMOSIN FRACTION V.

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Dept. Foods and Nutrition, Purdue Univ., West Lafayette, IN, 47907

Cancer Res; 42(6):2139-2145 1982

Moderate protein malnutrition retarded the ip proliferation of L1210 mouse leukemia cells in BALB/c mice. The increased resistance against leukemia cell growth in protein-malnourished mice was correlated with increased in vitro mitogenic responsiveness of spleen lymphocytes to phytohemagglutinin and increased levels of serum corticosterone but could not be correlated with altered development of splenic lymphocyte-mediated cytotoxicity. The increased resistance against leukemia cells in well-fed mice treated with thymosin alone could not be correlated with an increase in any of these parameters. Treatment with Thymosine Fraction V further increased the resistance of protein-malnourished mice to ip leukemia cell growth. The increased resistance of these mice to tumor cell growth was correlated with increased splenic lymphocyte mitogenic responsiveness to phytohemagglutinin, elevated serum corticosterone levels, and a slight increase in lymphocyte-mediated cytotoxicity 14 days after tumor challenge. For 7 days after the last treatment, protein-malnourished mice had reduced serum corticosterone levels. Nevertheless, the serum corticosterone levels were still higher than normal in these mice. (Author abstract) (34 Refs)

67. ANTI-TUMORAL EFFECT OF THYMOSIN FRACTION V PREINCUBATED NORMAL SYNGENEIC BONE MARROW CELLS (MEETING ABSTRACT)

Cupissol D, Rey A, Favier F, Goldstein AL, Serrou B
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VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

We have previously shown that thymosin fraction V preincubated normal syngeneic bone marrow cells can decrease the tumor growth of tumor bearing mice and increase significantly the survival time. In the present study we were able to show that 1) This effect disappeared when bone marrow cells were pre-treated in vitro with an anti-Thy 1-2 antiserum 2) This effect was not dependent of NK (natural killer) cells. In effect, we did not observe any change in anti-tumoral activity after in vivo treatment of mice by radioactive strontium which deletes NK cell activity. 3) This effect disappeared after bone marrow cell treatment by an antiserum Lyt 1 and was persistent after treatment by anti-serum Lyt 2-3. 4) The tumor decreased by the combined effect of thymosin fraction 5 and Cis-Platinum (CDDP) treatment in methylcholanthrene tumor bearing mice. This effect was significant as compared to the control group or the use of CDDP alone or thymosin alone. These results are sufficiently encouraging to support a clinical trial in advanced cancer patients, using this model, which is now in progress. (no Refs)

68. EFFECT OF THYMOSTIMULIN ON ACTIVITY OF CERTAIN ENZYMES OF ADENOSINE AND AMP METABOLISM IN RAT LYMPHOCYTES DURING MAMMARY GLAND CARCINOGENESIS.

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Res. Roentgenoradiological and Oncological Inst., Kiev, USSR
Ukr Biokhim Zh; 54(2):154-158 1982

The effect of thymostimulin (TS) on metabolism of adenosine and AMP was studied in random-bred female rats with dimethylbenz(a)anthracene induced mammary gland tumors. Animals received nine injections of TS with 10-day interval between the injections; total dose of TS was 9 mg/rat. In thymus lymphocytes of intact rats, TS produced a 1.3x increase of adenosine deaminase (ADA) activity, 1.6x decrease of 5'-nucleotidase activity, and 1.4x decrease of AMP-aminohydrolase (AH) activity. In spleen lymphocytes, TS administration resulted in a 1.5x decrease of adenylate kinase (AK) activity. The latent period of mammary gland carcinogenesis was characterized by the decrease of ADA, AK, and 5'-nucleotidase activities on day 10 followed by an increase of the activities of the enzymes tested on day 30. TS administration during the latent period of mammary gland carcinogenesis resulted in the decrease of all enzymes tested. These findings indicate that administration of thymosin-like substances can stimulate the functional activity of immunocompetent cells in animals with precancerous conditions. (17 Refs) (In RUS)

69. SERUM-FREE CULTURE OF RESTING, PHA-STIMULATED, AND TRANSFORMED LYMPHOID CELLS, INCLUDING HYBRIDOMAS.

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Exp Cell Res; 138(2):287-295 1982

A chemically-defined medium containing casein, insulin, testosterone, transferrin, and linoleic acid (CITTL) has been developed for the culture of lymphoid cells. Resting human mononuclear leukocytes can be maintained in CITTL for up to 8 wk with excellent viability. In the absence of mitogen, undifferentiated monocytes become the predominant cell type by 7-11 days as assessed by morphology, population distribution of cell sizes, and fluorescence-activated cell sorter analysis. Phytohemagglutinin (PHA)-induced proliferation is retained in these cultures for 7-10 days and results in a population of 85% T lymphoblasts. T lymphoblasts survive for 2 wk in CITTL following mitogenic stimulation and proliferate for up to 5 wk in CITTL if supplemented with 2-mercaptoethanol and conditioned medium containing crude T-cell growth factor. In addition to supporting proliferation of normal lymphoid cells, CITTL also sustains growth of human and murine hybridomas, as well as a variety of transformed lymphoid cell lines. The ability of a minimum essential medium supplemented with five or six factors to support growth of normal and malignant lymphoid cells suggests that only a limited number of extracellular signals are required for mitogenesis of these cells. (Author abstract) (49 Refs)

EFFECTS OF ENDOGENOUS AND EXOGENOUS AGENTS ON NON-STEROID HORMONE ACTIVITY

70. SECRETION OF CALCITONIN AND PARATHYROID HORMONE BY EMBRYONAL CARCINOMA CELLS: VARIATIONS WITH DIFFERENTIATION (MEETING ABSTRACT)

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Pediatr Res; 15(12):1552 1981

Differentiation of teratocarcinoma cells in culture allows us to study certain aspects of the early embryogenesis. The adenylate cyclase system of cultured F9 cells is specifically stimulated by calcitonin. Differentiation into endodermal cells by treatment with retinoic acid is followed by a loss of calcitonin responsiveness and the appearance of parathyroid hormone stimulation of the cyclase system. In addition radioimmunological and biological active forms of calcitonin are secreted by F9 cells in the culture medium. Along with differentiation with retinoic acid a progressive decrease of calcitonin secretion is observed: after 4 days of treatment calcitonin is no longer detectable. But at this stage of differentiation a parathyroid hormone-like substance is radioimmunologically and biologically detectable. These specific changes in hormonal secretion and receptivity can be used as markers of differentiation. These results also suggest a possible role for Calcitonin and Parathyroid hormone-like activities during the initial steps of embryogenesis. (no Refs)

71. PHENOTHIAZINE EFFECTS ON GONADOTROPIN-RESPONSIVE LEYDIG TUMOR CELLS (MEETING ABSTRACT)

Melner MH, Zimniski SJ, Puett D
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Fed Proc; 41(3):885 1982

These studies were undertaken to examine the effects of two phenothiazines, chlorpromazine (CP) and trifluoperazine (TFP), on adenylate cyclase (AC) activity and steroidogenesis in murine M5480A Leydig tumor cells. TFP is a potent inhibitor of many calmodulin-mediated processes, while CP has a much lower efficacy. Using dispersed Leydig tumor cells in primary culture, TFP (0.1-25 uM) inhibited both basal and human choriogonadotropin (hCG)-stimulated testosterone production. In contrast, CP at similar doses stimulated testosterone production. Moreover, the effects of the combination of CP and a maximal dose of hCG were additive in terms of androgen production. In particulate membrane fractions, TFP inhibited 5'-guanylimidodiphosphate [Gpp(NH)p]-stimulated AC activity both with and without hCG. On the other hand, CP stimulated AC activity in the presence of Gpp(NH)p, but did not alter the enzymic activity in the presence of maximal stimulatory doses of Gpp(NH)p (10 uM) and hCG (0.1 uM). Thus, in general the effects of the drugs on AC activity paralleled those in steroidogenesis. It is noteworthy that the two phenothiazines exhibit quite different actions on these two parameters and may prove useful in elucidating regulatory mechanisms in steroidogenesis. (no Refs)

72. THE EFFECTS OF CYCLOPHOSPHAMIDE AND ITS DERIVATIVES ON ADENYLATE CYCLASE ACTIVITY AND PROTEIN SYNTHESIS (MEETING ABSTRACT)

Fitton LA, Hunter GJ, Swoboda BE
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Br J Cancer; 44(2):306 1981

Nitrogen mustard chemotherapeutic agents are considered to obtain their effect by cross-linking DNA, though other cellular targets have been implicated. We have examined the effects of cyclophosphamide (CP) and its metabolites on the enzymes of cyclic-nucleotide metabolism and protein synthesis. CP, 4-ketocyclophosphamide (KP) and phosphoramide mustard (PM) (less than or equal to 15 mmol/l) were found to have no effect on basal or stimulated hepatic adenylate cyclase activity. 4-hydroperoxy-cyclophosphamide (HP, 5 mmol/l), was found to inhibit enzyme activity (50%) and completely abolished the effect of glucagon but only partially abolished the stimulatory effect of fluoride. Whereas CP and KP are 'inactive', PM is a potent alkylating agent and is considered as the 'ultimate' alkylating metabolite of CP. These results may be explained by the unique reactivity of HP. Similar specificity has been observed in the sensitivity of cAMP phosphodiesterase and protein kinase for HP. In a separate series of experiments, we have found that protein synthesis is inhibited by low concentrations of CP metabolites. HP (10 mmol/l), inhibited protein synthesis in rabbit reticulocyte lysate by 50%. PM and HN2 showed only a slight effect at this concentration (up to 10% inhibition). (3 Refs)

73. A RAT MODEL FOR MOPP INDUCED MALE INFERTILITY (MEETING ABSTRACT)

Glode LM, Gould SF, Nett T, Powell D
University of Colorado Health Sciences Center, Denver, CO, 80262
Proc Am Assoc Cancer Res; 23:878 1982

Procarbazine and/or alkylating agent therapy results in a high incidence of sterility among young male patients. To begin study of possible modes of protection from this toxicity, we examined the effect of chronic cyclophosphamide (C) and procarbazine (P) administration on body weight, testosterone and luteinizing hormone (LH) levels, and the spermatogenic epithelial histology of adult rats. Five animals/group received C or P at dose rates of 1-30 mg/Kg daily or 10-200 mg/Kg weekly. Sacrifices were performed at regular intervals, and testes prepared for routine light microscopic examination. Therapy stopped at day 84. P produced a dose dependent, permanent destruction of spermatogonia. C produced significantly less testicular germinal cell loss. C inhibited normal weight gain while P resulted in selective testicular weight loss. No consistent changes in Testosterone or LH were detected. These data indicate that P may be used to induce 'permanent' infertility in rats which is histologically identical to the lesion seen in man. (no Refs)

74. THYROID ACTIVITY DURING HEPATOCARCINOGENESIS BY N-2-FLUORENYLACETAMIDE IN THE MALE RAT.

Aussel C, Lafaurie M, Castelli D, Formento JL, Stora C
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Res Commun Chem Pathol Pharmacol; 36(1):105-117 1982

During chemical hepatocarcinogenesis by N-2-fluorenylacetamide, the hormonal status of male Sprague Dawley rats is modified. The histological study of the thyroid gland demonstrates a decreased activity evidenced by an augmentation of the follicle size and a reduced size of follicular epithelium. The level of T3 and T4 reflects in part this decreased activity. Comparison with female rats treated in the same conditions shows an opposite effect of N-2-fluorenylacetamide. Indeed in the female, the thyroid gland presented an hyperactive state accompanied by a drastic decrease of serum T3 and T4. This difference in thyroid activity might take an important part in the mechanism responsible for the sex difference in liver cancer induction by N-2-fluorenylacetamide. (Author abstract) (19 Refs)

75. MOLECULAR MECHANISMS OF ACTIVITY OF HORMONE-LINKED CYTOSTATICS.

Belousova AK, Boguslavskaia OA, Bergol'ts VV, Shkodinskaia EN, Kurdiumova KN
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(2):41-46 1982

The effect of steroid carrier on the alkylating activity of distrone (ester of chlorophenacyl and androgen) and phenthyrine (a derivative of thyronine) was studied in mice bearing ascites sarcoma 37. Analysis of single-stranded breaks and cross-links in DNA molecule showed that the alkylating activity of distrone was approx 10x lower than that of chlorphenacyl. Distrone caused marked and prolonged inhibition of 3H-androgen binding with chromatin from cells of the ventral prostate, while chlorophenacyl did not affect the nuclear acceptor sites. Phenthyrine caused a 40-70% inhibition of labeled triiodothyronine binding with cellular receptors. (30 Refs) (In RUS)

RECEPTOR/ BINDING SITES

76. SOLUBILIZATION OF EPINEPHRINE-SPECIFIC ALPHA2-ADRENERGIC RECEPTORS FROM ADRENOCORTICAL CARCINOMA.

Nambi P, Aiyar NV, Sharma RK
Dept. Biochemistry, Univ. Tennessee, Memphis, TN, 38163
FEBS Lett; 140(1):98-102 1982

Using a zwitterionic detergent, alpha-receptors were selectively solubilized from adrenocortical carcinoma 494. The isolated receptors were determined to be exclusively of the alpha2-subtype. A major function of these receptors may be the mediation of epinephrine-induced transmembrane signal via the activation of guanylate cyclase. The alpha2-adrenergic coupled guanylate cyclase system might be one of the means of transmitting the catecholamine-sensitive biological response in the adrenocortical carcinoma cell. (27 Refs)

77. DETECTION OF HUMAN MELANOMA MARKERS USING TYROSINASE ACTIVITY, ALPHA-MSH RECEPTORS AND MONOCLONAL ANTIBODIES (MEETING ABSTRACT)

Libert A, Arnould R, Ghanem G, Vercammen-Grandjean A, Lejeune FJ

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VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

In order to develop specific tumor markers, the authors undertook a study on enzymatic, hormonal and immunological properties from surgical specimens and on melanoma cell cultures. Tyrosinase was chosen as a specific enzyme of melanogenesis. Data from a radioenzymatic assay indicate that high tyrosinase activity is present in both pigmented primaries and subcutaneous metastasis, while achromic metastasis and cell cultures show minimal enzyme activity. 125I-alpha-Melanocyte Stimulating Hormone, a specific pituitary polypeptidic hormone was assayed for receptivity. Results indicate that some fresh melanoma cell cultures and cell lines have a significant receptivity for alpha-MSH. Anti-melanoma monoclonal antibodies, were tested on various melanoma lines and on unrelated tumor cell lines. Results from a 125I-Protein A assay demonstrate that many melanoma cell lines have antigenic determinants specific for malignant melanoma. (no Refs)

78. PROLACTIN RECEPTORS IN HUMAN BREAST TUMORS.

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JNCI; 68(3):381-383 1982

Prolactin-binding sites were determined in 759 human breast tumor biopsy specimens. Ovine prolactin (oPRL) was used in the binding assay of 659 tumors with 13% of the tumors showing a positive content with more than 1% specific binding. Human prolactin (hPRL) was utilized for 343 tumors with 36% of the tumors binding 1% or greater of the added radioactivity. When human growth hormone (hGH) was used as the labeled ligand in 95 tumors, only 2% of the tumors specifically bound more than 1% of the hGH. A total of 153 tumors were assayed simultaneously with the use of labeled hPRL and oPRL. Whereas 10.4% of the tumors showed the presence of prolactin-binding sites (greater than 1% specific binding) when oPRL was used, an approximately threefold increase (29.4%) in tumors possessing prolactin receptors was revealed when hPRL was used as the labeled ligand. Therefore, hPRL is the preferred ligand for the assessment of prolactin receptor levels in human breast cancer biopsy specimens. (Author abstract) (15 Refs)

79. MEMBRANE MICROVISCOSITY INCREASES IN REGRESSING NITROSOMETHYLUREA (NMU) INDUCED MAMMARY CARCINOMA (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:938 1982

The objective of these studies was to determine if the changes observed in prolactin-binding capacity of membranes from growing and regressing NMU induced mammary carcinoma correlated with those observed in membrane microviscosity measurements. Buffalo female rats were intravenously injected with 5 mg/100 g body weight of NMU at 50, 80 and 110 days of age. Mammary tumors induced in Buffalo rats by treatment with NMU are known to regress after oophorectomy. These rats were, therefore, either sham operated or oophorectomized at 5 months of age and sacrificed at 1, 3, 4, 5 and 8 days after the surgery. The 100,000 x g membrane pellets of these growing or regressing tumors were used for oPRL binding and fluidity studies. Membrane microviscosity was studied by fluorescence polarization at 24 C using a lipid probe 1,6 diphenylhexatriene (1 uM in PBS at pH 7.1). A 46% decrease in prolactin-binding capacity was observed in membranes obtained from animals sacrificed 8 days after oophorectomy. Such a decrease in prolactin binding capacity of membranes from regressing tumors is well documented. Fluorescence polarization values were low in membranes from growing tumors which increased progressively with time after oophorectomy, reaching a maximal value at 5 days after oophorectomy, the values being 0.140, 0.188, 0.226, 0.227, 0.248 and 0.250, for membranes from growing tumors and 1, 3, 4, 5 and 8 days regressing tumors, respectively. A similar difference in membrane fluorescence polarization values was observed in growing and regressing DMBA-induced mammary carcinoma. (no Refs)

80. DBA/2HA MICE AS A MODEL OF AN X-LINKED IMMUNODEFICIENCY WHICH IS DEFECTIVE IN THE EXPRESSION OF TRF-ACCEPTOR SITES(S) ON B LYMPHOCYTES.

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Immunol Rev; 64:25-55 1982

An experimental system for analyzing functional properties of TRF-producing helper T cells and the genetic basis for the activation of B cells by TRF acceptor sites(s) using the DBA/2Ha mouse strain is described. Evidence that two distinct subpopulations of helper cells exist, one which collaborates with B cells with cognate interactions and the other which releases TRF and is genetically unrestricted in its interaction with B cells, is presented. The expression of TRF acceptor sites on the B cells is controlled by the X-chromosome-linked recessive genes. Two distinct subpopulations of B cells which differ in their activation requirements exist. (93 Refs)

OTHER RELATED STUDIES

81. PROTON-TRANSLOCATING MG2+-DEPENDENT ATPASE ACTIVITY IN INSULIN-SECRETORY GRANULES.

Hutton JC, Peshavaria M
Dept. Clinical Biochemistry, Univ. Cambridge, New Addenbrooke's Hosp., Hills Road, Cambridge CB2 2QR, England
Biochem J; 204(1):161-170 1982

Insulin-secretory granules isolated from a pancreatic islet-cell tumor by centrifugation on Percoll density gradients exhibited a membrane-associated MG++-dependent ATPase activity. In granule suspensions incubated in iso-osmotic media, activity was increased two to three-fold by carbonyl cyanide p-trifluoromethoxyphenylhydrazone, the combination of valinomycin, nigericin and K2SO4 or by the addition of a detergent. Permeant anions also increased Mg++-dependent ATPase activity under iso-osmotic conditions when combined with K+ and nigericin, or NH4+. It was deduced that a major component of the activity was coupled to the translocation of protons into the granule interior. The granule membrane appeared poorly permeable to H+, K+, NH4+ and SO4-- but permeable, in increasing order, to phosphate or acetate, Cl-, I- and SCN-. Like the proton-translocating ATPase of mammalian mitochondria the granule enzyme when membrane-bound was inhibited by up to 85% by tributyltin or NN'-dicyclohexylcarbodi-imide and was solubilized in a tributyltin-insensitive form after extraction with dichloromethane. It was clearly not a mitochondrial contaminant as evidence by the distribution of marker proteins on density gradients. Unlike mitochondrial activity it was insensitive to oligomycin, efrapeptin, atractyloside, azide and oxyanions. Its properties, however, were indistinguishable from those of the proton-translocating ATPase found in the chromaffin granules of the adrenal medulla. Moreover, insulin granules and chromaffin granules exhibited similar levels of activity. This indicated that in spite of the differences in their internal composition, granules from tissue involved in polypeptide and amine hormone secretion possess catalytic components in common. Only a minor role for the ATPase in amine transport in insulin granules was apparent. Rather, its presence here may relate to the process of secretory vesicle morphogenesis or to the exocytotic mechanism. (Author abstract) (42 Refs)

82. THE INTERNAL PH AND MEMBRANE POTENTIAL OF THE INSULIN-SECRETORY GRANULE.

Hutton JC
Dept. Clinical Biochemistry, Univ. Cambridge, New Addenbrooke's Hosp., Hills Road, Cambridge CB2 2QR, England
Biochem J; 204(1):171-178 1982

The membrane potential (delta psi) and the pH gradient (delta pH) across the membrane of the insulin-secretory granule were determined in studies in vitro from the uptake of the permeant anion thiol[14C]cyanate or the permeant base [14C]methylamine. Freshly prepared granules incubated in iso-osmotic medium containing sucrose and low concentrations of buffer salts exhibited an acidic internal pH and a delta psi positive inside. Addition of MgATP-- under these conditions did not alter the delta pH, but produced a marked increase in the delta psi. Conversely, when a permeant anion was also included, ATP produced a marked increase in the delta pH and a lesser increment in the delta psi. NH4+ salts reduced the delta pH across granule membranes. In the presence of ATP this effect was accompanied by a reciprocal increase in the delta psi. A similar reciprocity was evident when nigericin was added together with K+ or on decreasing the medium pH, suggesting that these gradients were linked by a common electrogenic process. The effects of ATP were reversed by the protonophore carbonyl cyanide p-trifluoromethoxyphenylhydrazone, the combination of valinomycin, nigericin and K+, and by the Mg++-dependent ATPase inhibitor tributyltin. Uptakes of 14C-labeled tracer molecules were also markedly reduced by cryogenic disruption of the granule membrane or hypo-osmotic incubation conditions. These results were readily interpreted within a chemiosmotic hypothesis, which proposed that the insulin granules possess an inwardly-directed electrogenic proton-translocating Mg++-dependent. ATPase with the additional postulate that the membrane has a low proton permeability. The intragranular pH was estimated as being between 5 and 6 in vivo. Such a value corresponds to optimal conditions for the crystallization of zinc-insulin hexamers. Several other functions related to chemiosmotic processes within insulin granules, however, may be envisaged. (Author abstract) (28 Refs)

83. ANTIBODY-FOCUSED PEROXIDE-MEDIATED TUMORICIDAL ACTIVITY IN ATHYMIC MICE (MEETING ABSTRACT)

Beyerle MP, Arnold RR
University of Louisville, Louisville, KY, 40292
Fed Proc; 41(3):803 1982

Preliminary studies have shown that tumor-specific antibody conjugated to a peroxide-generating enzyme can focus the tumoricidal activity of the lactoperoxidase system in vitro. The present studies were designed to determine if an antibody-enzyme conjugate could potentiate the tumoricidal system in vivo. The human choriocarcinoma (JEG-3) was maintained as a monolayer in Ham's F12 with 5% FCS (fetal calf serum). Cells were removed by gentle scraping, washed and resuspended in Dulbecco's PBS phosphate-buffered saline without glucose. Cells were incubated at 37C/30 min in either PBS; bovine anti-human choriogonadotropin (HCG), or anti-HCG conjugated with glucose oxidase (GO); washed and resuspended in PBS. The various cell preparations were injected sq into the flank of congenitally athymic (nu/nu) Swiss-Webster mice. Visible tumor growth was detected in all recipients of either PBS or anti-HCG treated cells, usually within two weeks. There were no detectable tumors in the recipients of anti-HCG-GO treated cells for 2 months post injection and 3 of 5 remained tumor-free. These data suggest that anti-HCG-GO can stimulate peroxidase-dependent tumoricidal activity of athymic mice against an HCG-bearing tumor line, since the antibody conjugate required peroxidase and halide for in vitro killing and unconjugated anti-HCG did not inhibit in vivo tumor growth. (no Refs)

84. BIOLOGICAL BEHAVIOR OF MM1 HAMSTER MELANOMA.

Stanberry LR, Das Gupta TK, Beattie CW
(c/o Beattie) Div. Surgical Oncology, Dept. Surgery, Univ. Illinois Medical Center, P.O. Box 6998, Chicago, IL, 60680
Cancer Res; 42(6):2238-2241 1982

We have reported evidence recently for a high-affinity receptor for glucocorticoid Malignant Melanoma Number 1 hamster melanoma and suggested that tumor growth was facilitated by adrenal steroids. This report characterizes the behavior of Malignant Melanoma Number 1 following manipulation of the pituitary-adrenal axis in vivo. Bilateral adrenalectomy significantly retarded tumor growth. Hypophysectomy also significantly reduced tumor growth. Silastic implants of hydrocortisone in intact hamsters produced a dose (7 to 28 ug/day)-related increase in tumor growth. Implants releasing a low dose (3 ug/day) of dexamethasone also increased tumor growth. Chronic exposure of adrenalectomized and intact hamsters to a high dose (125 ug/day) of desoxycorticosterone acetate also produced a significant increase over adrenalectomized and sham-adrenalectomized controls. In contrast, chronic administration of adrenocorticotrophic hormone and alpha-melanocyte-stimulating hormone to intact hamsters did not significantly alter melanoma growth. These observations support the suggestion that adrenocorticosteroids influence the growth of Malignant Melanoma Number 1 hamster melanoma and provide a model for studying the regulation of growth of a glucocorticoid-positive neoplasm originating outside the reticuloendothelial system. (Author abstract) (33 Refs)

85. CONTROLLED RELEASE OF MACROMOLECULES.

Langer R
Massachusetts Inst. Technology, Cambridge, MA, 02139
Chemtech; 12(2):98-105 1982

Systems for controlled effusion of large molecules (mol wt greater than 1,000) such as polypeptide hormones, polysaccharides, antigens, antibodies, and others (eg, interferon) are reviewed. Drug-polymer matrix ultrastructure, constant (zero-order) release, magnetic modulation of drug release, bioassays, and potential clinical applications are discussed. Macromolecular drugs such as growth hormones and the isolation of potent informational molecules, such as endorphins, enkephalins, luteinizing hormone-releasing hormone, and interferon, are likely to require controlled release delivery systems. (44 Refs)

86. DISTURBANCES IN TEMPERATURE REGULATION IN ENDOCRINE DISEASES.

Benker G
Medizinische Klinik und Poliklinik, Universitat Essen, Hufelandstrasse 55, 4300 Essen, W. Germany
Therapiewoche; 32(11):1494-1500 1982

Studies on disturbances in body temperature regulation in patients with endocrine diseases are reviewed. Tumors of the pituitary gland or hypothalamus can cause disturbances in temperature regulation, but fever or hypothermia are seldom cardinal symptoms of these tumors. Epinephrine-secreting pheochromocytomas often cause increased heat production due to enhanced glycogenolysis and lipolysis. Hyperpyrexia was assumed to be the cause of death in 4% of 72 patients with pheochromocytomas who were not subjected to surgery. (27 Refs) (In GER)

87. PARANEOPLASTIC SYNDROMES.

Minna JD, Bunn PA
Div. Cancer Treatment, Navy Medical Oncology Branch, NCI, Natl. Naval Medical Center, Bethesda, MD
Cancer - Principles and Practice of Oncology. DeVita VT, Hellman S, and Rosenberg SA, ed. Philadelphia, Lippincott, 1926 pp., 1982.

Paraneoplastic syndromes (PNS) are remote effects of neoplasms, not caused by a direct action of the tumor or its metastases. The following areas are discussed: etiology and pathogenesis; endocrinologic, neurologic, and hematologic manifestations of malignancy; and anemia and thrombocytosis associated with cancer. The true frequency of PNS is difficult to determine. Some syndromes usually caused by a neoplasm or its treatment (eg, cachexia) can be identified as PNS because the symptoms appear before the cancer is diagnosed and subside when the tumor is successfully treated. The course of a PNS may be independent of the tumor's course; a neurologic PNS may be unaffected by treatment because the neurologic damage is irreversible. Causes of PNS include: the tumor's production of biologically active proteins or polypeptides; autoimmunity; immune complex production and suppression; 'ectopic receptor' production (or competitive inhibition of normal hormone action by tumor-produced, biologically inactive hormones); and 'forbidden contact' (in which enzymes or other products that do not normally circulate are released into the circulation because of the tumor's vascular or other abnormalities). Some PNS of unknown origin may be related to the tumor's production of substances as yet unidentified. Some syndromes are so strongly associated with cancer that their occurrence in a patient with no known malignancy should prompt a search for cancer. (430 Refs)

88. EXTINCTION OF HORMONE-DEPENDENT MAMMARY CANCER IN VIVO AND IN VITRO BY CHLOREA TOXIN (MEETING ABSTRACT)

Clair T, Shepheard C, Cho-Chung YS
National Cancer Institute, National Institutes of Health, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:912 1982

Growth of 4,12-dimethylbenz(a)anthracene (DMBA) induced mammary carcinoma in rat was arrested by daily SC injections of cholera toxin, the exo-enterotoxin of the bacterium Vibrio Cholerae. At a dose of 2 ug/200 g rat, tumors regressed to 50% of their initial size within 2-3 weeks and 85% of tumors regressed completely within 4-6 weeks. The same response to cholera toxin was observed with other hormone-dependent mammary tumor, MTW9, but not with hormone-inedpendent tumors, DMBA number 1 and MT 13762. The latter result was consistent with the lack of response of these hormone-independent tumors to hormone-removal (ovariectomy) or dibutyryl cyclic AMP treatment. The growth inhibitory effect of cholera toxin was dose-dependent and upon cessation of treatment tumors resumed growth; after complete regression, however, tumors did not reappear until 6 months of after termination of the treatment. The amount of cholera toxin as high as 10 ug/day/ 200 g rat injected over 6 weeks period was not toxic to the animals. The growth of human breast cancer cells (MCF-7), in vitro was also inhibited by a daily supplement of cholera toxin. At a concentration of 100 ng/ml, the cell replication ceased completely within 2 days and 1 ng/ml exhibited 50% growth inhibition by day 2. The growth inhibitions of both in vivo and in vitro were preceded by marked increases in the cellular cyclic AMP content, adenylate cyclase, and type II cyclic AMP-dependent protein kinase activities as well as a decrease of estrogen binding activity. Thus, extinction of mammary cancer can be achieved by cholera toxin, an agent that increases intracellular cyclic AMP. (no Refs)

89. INHIBITION OF THYMIDINE UPTAKE OF TUMOR CELLS BY PLATELET LYSATE (MEETING ABSTRACT)

Landolfi R, Steiner M
Division of Hematologic Research, The Memorial Hospital, Pawtucket, RI, 02860
Fed Proc; 41(3):334 1982

Platelets are known to contain growth factors for normal and tumor cells. We have studied the effect of human platelet lysate (HPL) on the incorporation of [3H]-thymidine by mouse neuroblastoma (Neuro-2a) cells. Actively growing Neuro-2a cells were pulse labeled with [3H]-thymidine at various concentrations (0.012-0.05 nmol/ml). Thymidine incorporation into DNA was measured by preparing a perchloric acid extract of the tumor cells. Addition of HPL produced a maximal reduction of thymidine incorporation ranging from 38-51% which was independent of the thymidine concentration used. A linear dose dependency of the suppressant effect of HPL was demonstrated up to about 100 ug protein/ml. In other experiments Neuro-2a cells, synchronized in G1 by serum deprivation, were continuously exposed to low concentration of [3H]-thymidine (2.5 pmol/ml) for up to 48 hours. HPL inhibited [3H]-thymidine incorporation by 81-88% compared to controls. The presence of fetal calf serum up to 10% was unable to overcome the inhibition exerted by HPL. Removal of HPL from the medium completely restored normal thymidine uptake. The inhibitor was found to be non-dialyzable, heat sensitive (75C for 30 min) and acid resistant (pH 4.5). A MW of approximately 100,000 was estimated by gel filtration. These findings show that platelets contain both positive and negative modulators of tumor cell growth. (no Refs)

90. MENOPAUSE.

Cohen AW
Univ. Pennsylvania Sch. Medicine, Philadelphia, PA
Del Med J; 54(4):227-230 1982

The progression of changes that occur during perimenopause is discussed. The perimenopause or climacteric is associated with adjustments in estrogen, follicle-stimulating hormone, and luteinizing hormone; changes in physiology and appearance; and psychological reactions to aging. Estrogen replacement therapy aids in control of vasomotor reactions, reduces emotional response to the climacteric, and offers opportunities for prevention of osteoporosis. Each patient requires individualized treatment. Agents such as beta-adrenergic blockers, tranquilizers, and the antihypertensive clonidine may be appropriate for some patients. (13 Refs)

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CHARACTERIZATION OF NON-STEROID HORMONES IN EXPERIMENTAL AND IN VITRO SYSTEMS

1. DISAPPEARANCE RATE OF ENDOGENOUSLY RADIOIODINATED THYROGLOBULIN AND THYROXINE AFTER RADIOIODINE TREATMENT.

Jeevanram RK, Shah DH, Sharma SM, Ganatra RD
Radiation Medicine Centre, Bhabha Atomic Res. Centre, Tata Memorial Centre Annexe, Parel, Bombay-400 012, India
Cancer; 49(11):2281-2284 1982

Endogenously radioiodinated thyroglobulin (tg) and thyroxine (T4), in the circulation following, therapeutic doses of radioiodine were studied in five patients with differentiated thyroid carcinoma. Radioactive serum was fractionated on a Sephadex G-200 and the various radioactive peaks thus obtained were analyzed for their biochemical and immunologic characteristics using precipitation with trichloroacetic acid (TCA) and antithyroglobulin antibody extraction with acidified n-butanol and electrophoresis on agar gel. The disappearance rates of endogenously labeled tg and T4 were 3.12 +-0.396 days and 10.14 +-1.81 days, respectively. (Author abstract) (16 Refs)

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2. HETEROGENEITY OF PLASMA AND URINARY IMMUNOREACTIVE CALCITONIN IN PATIENTS WITH MEDULLARY CARCINOMA OF THE THYROID.

Morimoto S, Okada Y, Onishi T, Takai S, Miyauchi A, Lee S, Nishioka Y, Kumahara Y
Dept. Medicine and Geriatrics, Osaka Univ. Medical Sch., Fukushima-ku, Osaka 553, Japan
Endocrinol Jpn; 28(5):583-594 1981

Disappearance of the calcitonin (CT) forms from the blood after calcium infusion (CAI) and total thyroidectomy, and the relation of urinary and plasma CT were studied in two female patients (14 yr old, patient A; 65 yr old patient B) with medullary carcinoma of the thyroid. The two antisera (antiserum I and antiserum II) had similar binding affinities for (1-32)human CT (hCT) monomer. Antiserum I appeared to have a major antigenic site within residues 21-32 of hCT monomer and a minor antigenic site within residues 21-32 of hCT, while the antiserum II appeared to have a major antigenic site within residues 11-16 and a minor antigenic site within residues 17-20. In all samples, values for immunoreactive hCT concentration measured by immunoassay with antiserum I were 1.08-1.79x higher than those measured by immunoassay with antiserum II. Immediately after CAI, the serum calcium level increased from 9.0 to 10.8 mg/deciliter (dl) in patient A and from 9.2 to 11.2 mg/dl in patient B. The plasma hCT level increased to 10.6 and 9.6x the initial level in patient A, and to 11.9 and 12.0x the initial level in patient B, as estimated with antiserum I and II, respectively. Very high levels of immunoreactive CT levels were found in the urine of both patients. The elution patterns of the basal plasma samples of both patients on the Bio Gel P-30 column are compared. In both patients, all forms of CT increased immediately after CAI. The level of immunoreactive CT in urine samples also decreased in both patients after thyroidectomy. Results indicated that serum CT in various forms including the monomer may be converted to form IIIb in the kidney and excreted in that form. (43 Refs)

3. IMMUNOPEROXIDASE STAINING FOR SEROTONIN, BOMBESIN, CALCITONIN, LEU-ENKEPHALIN IN PULMONARY TUMORLETS, BRONCHIAL CARCINOIDS, AND OAT CELL CARCINOMAS (MEETING ABSTRACT)

Cutz E, Chan W, Kay JM, Chamberlain DW
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Lab Invest; 46(1):16A 1982

Recent immunohistochemical studies identified serotonin and polypeptide hormones (bombesin, calcitonin, leu-enkephalin) in neuroendocrine (NE) cells of normal human lung. Although the precise function of NE cells in the lung is unknown, it has been suggested that they represent intrapulmonary hypoxia-sensitive chemoreceptors or endocrine/paracrine cells. Pulmonary NE cells are also considered to be the cells of origin for pulmonary tumorlets (PT), bronchial carcinoids (BC), and oat cell carcinomas (OCC). To determine whether these pulmonary lesions exhibit immunoreactivities similar to NE cells in normal lung, indirect immunoperoxidase (IP) method for serotonin, bombesin, calcitonin, and leu-enkephalin was applied on consecutive, formalin-fixed paraffin sections. The tissue blocks from cases of PT (seven), BC (11), and OCC (10) were retrieved from surgical or autopsy files. As positive controls, sections of normal lung were used. All cases of PT showed strong immunoreactivity for bombesin and serotonin. Typical cell nests within the bronchial epithelium, interstitium, or alveoli were diffusely positive. IP staining for calcitonin was also positive, but only some of the cells were stained. None of PT were immunoreactive for leu-enkephalin. Six cases of BC contained groups and/or single serotonin-immunoreactive cells, but none were positive for peptide hormones. Only in two cases of OCC were a few weakly serotonin-immunoreactive cells found, and all cases were negative for the three peptides tested. (no Refs)

4. COMMERCIAL IMMUNOPEROXIDASE KITS IN THE STUDY OF THIRTEEN PANCREATIC ISLET CELL TUMORS (MEETING ABSTRACT)

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Lab Invest; 46(1):15A 1982

The practicability of employing commerical immunoperoxidase kits for the study of gastrin, glucagon, insulin, and somatostatin production in 13 islet cell tumors was assessed. Using kits saves time in preparation and technique and is economical if used for occasional tests. The advantages of the immunoperoxidase technique include use of fixed paraffin-embedded tissue, good morphologic detail, and use of the light microscope. Results are reproducible with crisp immunostain and minimal background staining. The relevant hormone was specifically identified in seven symptomatic tumors (two gastrinomas, one glucagonoma, four insulinomas). Of six asymptomatic tumors, five showed strongly positive glucagon immunostain and one somatostatin. Nine tumors, in addition, contained somatostatin. Three tumors produced a third hormone. Normal distribution of peptide hormones in the positive control or adjacent pancreatic islets, and the varying distribution and intensity of immunostain for the four different hormones in each tumor, also indicated good specificity. The PAP (peroxidase-antiperoxidase) techniques. Intensity of immunostain was 2+ to 3+ in all except one gastrinoma and one insulinoma which showed weak focal positivity. Use of kits can prove expensive for large numbers or for single tests. Reagents supplied were of unknown dilution and usually insufficient. Occasionally, especially with insulin, sections floated, and immunostain was patchy and/or hazy. Fading of immunostain was noted after 6 months of storage. (no Refs)

5. ENKEPHALINS IN FUNCTIONING PANCREATIC ISLET CELL TUMORS: AN IMMUNOCYTOCHEMICAL SURVEY (MEETING ABSTRACT)

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Lab Invest; 46(1):17A 1982

Enkephalins or opiate receptor ligands, first detected in the brain, have not been immunohistochemically localized peripherally in the myenteric plexuses and nerve terminals of the gut. Recently, immunoreactivity to enkephalins has also been demonstrated in a subpopulation of the gastrin-producing G cells in the stomach and in the glucagon-producing A cells of the pancreatic islets. An immunocytochemical survey for localization of (Leu5)-Enkephalin-like immunoreactivity (LEI) in nine functional pancreatic islet cell tumors (six insulinomas and three gastrinomas demonstrated LEI within the tumor cells in three (two insulinomas and one gastrinoma). Although the presence of such immunoreactivity did not correlate with the benign or malignant nature of these tumors, it showed a positive correlation with their multihormonal character. The insulinomas, in addition to immunoreactivity to insulin and enkephalin, also showed immunoreactivity to gastrin and glucagon (one case each), whereas the gastrinoma showed focal immunoreactivity to both insulin and glucagon. Whereas 'heuronal' enkephalin is currently believed to have a regulatory role on gut motility, the exact biologic significance of the pancreatic 'cellular' enkephalin is unclear. (no Refs)

6. THYROTROPIN-PRODUCING PITUITARY ADENOMAS: AN IMMUNOHISTOCHEMICAL AND ULTRASTRUCTURAL STUDY (MEETING ABSTRACT)

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Lab Invest; 46(1):48A 1982

Thyrotropin (TSH)-producing adenomas are an uncommon variety of pituitary adenomas. Clinically, they may be associated with pituitary hyperthyroidism or they may arise in patients with long-standing hypothyroidism. The light microscopic, immunohistochemical, and ultrastructural features of TSH-producing pituitary adenomas from two clinically thyrotoxic patients are presented. These two 'chromophobe' macroadenomas were comprised of large polyhedral cells with irregular, occasional pleomorphic nuclei and infrequent mitosis. Immunoperoxidase staining revealed that many of the tumor cells contained moderate immunoreactivity for alpha and beta subunits of TSH (TSH-alpha, TSH-beta); these cells had polyhedral configuration and slender cytoplasmic processes with accentuation of immunoreactivity along the cell borders. A smaller population of tumor cells were immunoreactive for prolactin (PRL) and, in one adenoma, also growth hormone. Double immunoperoxidase staining revealed that the TSH-beta and PRL cells constituted two different cell populations. Ultrastructurally, the distinctive features were the presence of long cytoplasmic processes extending between neighboring cells and the margination of granules against the plasma members of both cell body and processes. Most of the tumor cells contained sparse secretory granules averaging 150 nm in diameter. Also, the tumor cells displayed evidence of secretory activity, with abundant rough endoplasmic reticulum, prominent Golgi apparatus, moderate number of mitochondria, and lysosomal bodies. (no Refs)

7. LOCALIZATION OF ALPHA-MELANOCYTE-STIMULATING HORMONE IN THE PITUITARY OF NORMAL HAMSTERS AND IN ESTROGEN-INDUCED PITUITARY TUMORS (MEETING ABSTRACT)

Finkelstein JA, Lee IM, Lotstra F, Steggles AW, Vanderhaeghen JJ
Northeastern Ohio Universities College of Medicine, Rootstown, OH
Anat Rec; 202(3):57A 1982

Immunocytochemistry was used to localize alpha-melanocyte-stimulating-hormone-like immunoreactivity (alpha-MSH) in the pituitary gland or normal hamsters and of hamsters with estrogen-induced pituitary tumors. The tumors were induced by subcutaneous implantation of diethylstilbestrol (DES). After nine months of treatment, experimental animals and age-matched controls were sacrificed. Pituitaries were fixed by immersion in Bouin's, embedded in paraffin and processed by the indirect peroxidase-anti-peroxidase technique, using an antibody to alpha-MSH. In the normal pituitary, alpha-MSH-containing cells formed a band between the neural lobe and the pituitary cleft and were completely co-extensive with the intermediate lobe. A few immunoreactive cells were seen in the anterior lobe either immediately adjacent to the intermediate lobe or scattered randomly. Treatment with DES produced enlarged pituitaries; sometimes it was difficult to distinguish clearly the three separate lobes of the pituitary. In other experimental animals in which the three lobes were definable, the enlargement was due to increased size of both the anterior and intermediate lobes, with a consequent compression of the posterior lobe. One effect of DES treatment in the intermediate lobe, was an increase in the number of alpha-MSH-containing cells which showed different intensities of staining; densely stained cells tended to be prominently organized around lumina. (no Refs)

8. MONOCLONAL ANTIBODIES TO AMINO TERMINAL AND TO CARBOXYL TERMINAL SEQUENCES OF BOVINE PARATHYROID HORMONE (MEETING ABSTRACT)

Wang IY, Roof BS, Kang S, Tung E, Yang J
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Med Pediatr Oncol; 10(1):103 1982

Cancers can produce parathyroid hormone (PTH) ectopically and be associated with elevated levels of circulating PTH. Antisera to PTH used in radioimmunoassays more commonly are developed to carboxyl (C) terminal than to amino (N) terminal peptide (containing biologically active sites). In order to investigate the PTH moieties produced by cancers, we have produced monoclonal antibodies to PTH using hybridoma technique. Two clones are established, one of which recognized the N-terminal peptide (1-34 amino acid residues), and one the C-terminal peptide (53-84 amino acid residues). One Balb/c mouse was immunized with bovine PTH and complete Freund's adjuvant over 9 months spleen cells of the mouse were fused with SP-2 mouse myeloma cells using 50% PEG 4000. Hybrid cells were selected with hypoxanthine-aminopterin-thymidine (HAT) medium. Culture fluids were screened for antibody production to PTH and to synthetic peptides of PTH. Antibody produced by Clone P-1 binds to the intact PTH and to N-terminal peptide. Antibody produced by Clone P-2 binds to intact PTH and to C-terminal peptide of PTH. Clone P-1 can be subcloned easier than Clone P-2. Each clone was subcloned twice. Characterization of the monoclonal antibodies by immunoelectrophoresis demonstrated Clone P-1 produced mouse immunoglobulins of IgG2a subclass; Clone P-2 produced IgG2b subclass immunoglobulins. Titers greater than 10,000 but lower than 100,000 were produced in sera and ascitic fluids of mice injected intraperitoneally with cells of either clone. Monoclonal antibodies to PTH have been successfully produced in mice. The monoclonal antibodies produced by Clone P-1 and Clone P-2 cells belong to different subclasses. These monoclonal antibodies may serve as useful reagents in measuring circulating PTH molecules as well as N- or C-terminal fragments of PTH molecules in patients. (no Refs)

9. PHEOCHROMOCYTOMA AND HYPOPHYSECTOMY: EFFECTS ON BLOOD PRESSURE AND CATECHOLAMINES (MEETING ABSTRACT)

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Life Sci; 30(7/8):601 1982

The New England Deaconess Hospital (NEDH) Wistar rat provides a valuable animal model for studying pheochromocytoma. Spontaneous pheochromocytoma occurs in NEDH rats, especially with aging; 59% of male rats 700 to 900 days old and 81% of rats 900 days old or older develop spontaneous pheochromocytoma. Tumors occur almost exclusively in the adrenal gland and 50% are bilateral. They may be readily transplanted into other NEDH rats and will cause hypertension, cardiovascular lesions, weight loss and death, usually within one month. Even without pheochromocytoma, by 11 1/2 weeks of age 75% of rats were moderately hypertensive whereas 25% remained normotensive; mean systolic blood pressure was 160+/-8 mmHg. Thereafter pressures increased only slightly until about 2 years of age when they become sharply elevated due to development of spontaneous pheochromocytoma in some rats. Although pheochromocytoma transplantation in unhypophysectomized rats caused blood pressure elevations to a range betwen 150 and 200 mmHg and usually caused death within 3 or 4 weeks, hypophysectomized NEDH rats remained normotensive or slightly hypotensive despite marked elevation of plasma norepinephrine and dopamine released from the tumor. In rats with tumor transplants plasma concentrations of dopamine and norepinephrine were respectively 100 times and 15 times that in control rats whereas epinephrine was only 3 times greater; concentrations of catecholamines in red blood cells were not significantly different from those in the plasma. Unlike the NEDH rat adrenal which contains epinephrine (76%) and norepinephrine (21%) with little if any dopamine, pheochromocytoma transplants contain mainly norepinephrine (72%) and dopamine (26%) with little if any epinephrine. It appears that these pheochromocytomas are deficient in the enzyme phenylethanolamine-N-methyltransferase (PNMT) which converts norepinephrine to epinephrine. (no Refs)

10. EVIDENCE FOR THE ROLE OF ANDROGENS IN THE FEEDBACK CONTROL OF GONADOTROPHIN SECRETION IN THE HUMAN FEMALE.

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S Afr Med J; 61(22):837-838 1982

The effect of androgens on the luteinizing hormone (LH) response to LH-releasing hormone (LH-RH) is fairly well documented. However, the evidence concerning the effect on follicle-stimulating hormone (FSH) is less convincing and clear-cut. We administered LH-RH to a patient with an androgen-producing adrenal tumor both before and after removal of the tumor. Before operation, testosterone levels were elevated and estradiol levels reduced. There was no response of either LH or FSH levels to LH-RH on two separate occasions. Postoperatively LH-FSH values rose sharply, to 404% and 170% above basal levels respectively. The data suggest that androgens do play a role in the feedback control of both LH and FSH secretion. (Author abstract) (11 Refs)

11. SUPEROXIDE RADICAL MEDIATED OXIDATION OF EPINEPHRINE BY TUMOR NUCLEAR MEMBRANES.

Peskin AV, Tarakhovskii AM, Shliakhovenko VA, Zbarskii IB
N. K. Kol'tsov Inst. Biology Development, Moscow, USSR
Dokl Akad Nauk SSSR; 263(5):1270-1273 1982

Superoxide radical formation in the nuclear membranes of various tumor cells (glioma 35, glioma 223, erythromyelosis, Pliss lymphosarcoma, Zajdela hepatoma) was studied. Analysis of superoxide dismutase (inhibiting epinephrine oxidation) showed that the rate of superoxide formation in tumor microsomes was lower than that in microsomes from normal tissues. The rate of superoxide formation in nuclear membranes of tumor cells exceeded that in nuclear membranes from normal tissues. (14 Refs) (In RUS)

12. MELANIN PRODUCTION IN A MEDULLARY THYROID CARCINOMA.

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Cancer; 49(12):2518-2526 1982

Melanin production by a medullary thyroid carcinoma (MTC) is reported and discussed. Immunohistochemically, the tumor cells contained calcitonin; by electron microscopy, they bore numerous, heterogenous granules similar to those described previously in MTCs. One small focus of tumor was pigmented. Here, melanosomes in different stages of maturation were found in dendritic cells that ramified among granule-bearing cells. The remarkable phenotypic divergence in this solitary, nongerm cell neoplasm is unusual but not so surprising in light of the APUD nature and neural crest origin of both the melanocyte and the thyroid C cell, which gives rise to MTC. The authors view the calcitonin and melanosome phenotypes as closely related tumor clones evolving from a common precursor neoplastic cell. This unique 'experiment of nature' adds to the set of rare human tumors that make melanin 'ectopically'. (Author abstract) (50 Refs)

13. BIOCHEMICAL AND METABOLIC ASPECTS OF PLATELET DYSFUNCTION IN CHRONIC MYELOPROLIFERATIVE DISORDERS.

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Thromb Haemost; 47(2):84-89 1982

Platelet content of serotonin (5HT) and adenine nucleotide, as well as 5HT uptake and storage were studied in 52 patients with myeloproliferative disorders (MPD). Thirteen patients had polycythemia vera (PV), 23 primary thrombocythemia (PT), 10 chronic granulocytic leukemia (CGL), and 6 myelofibrosis (MF). The bleeding time was prolonged in five patients, two with PT and three with MF. Decreased platelet adhesiveness was found in half of the PT, CGL, and MF patients, but only in 3/13 PV patients. ADP was significantly low in all MPD patients, the difference from controls being less marked in CGL patients. Platelet 5HT was reduced in patients with PT, PV, MF, and, to a lesser extent, with CGL. Patients with reactive thrombocytosis had normal 5HT contents. The rate and extent of 14C-5HT uptake in percent platelet radioactivity with a fixed platelet concentration were low in patients with PT, PV, and MF, but not in those with CGL. Thromboxane B2 (TxB2) production was normal in patients with PT and MF, and significantly increased in PV patients. Patients with CGL produced a lower amount of TxB2. ADP and 5HT were assayed in eight patients with PT after chemotherapy with busulfan and return to normal platelet count. The abnormally low values were found to persist. No significant changes were observed in five patients with PV after normalization of RBC counts following repeated phlebotomies. Results confirmed the platelet storage pool deficiency in patients with MPD, and suggested that biochemical abnormalities are related to the presence of abnormal clones in the bone marrow, thus resulting in the production of defective platelets. (42 Refs)

CLINICAL, DIAGNOSTIC AND PROGNOSTIC STUDIES

14. THYROTROPIC AND THYROID FUNCTION AFTER NEOPLASTIC TREATMENT OF INFANTS.

Mussa GC, Bona G, Cordero di Montezemolo L, Silvestro L, Italiano F, Ardissone P
Clinica Pediatrica IV, Universita degli Study di Torino, Torino, Italy
Minerva Pediatr; 34(4):151-159 1982

Forty cancer patients were divided into Group A, consisting of 18 patients (4-16 yr old) who had acute lymphoblastic leukemia (ALL), were treated with chemotherapy (CT) and cranial radiotherapy (RT: 2,400 rad), and were without such treatment for 5-48 mo, and Group B, consisting of 22 patients (1.5-16 yr old) who had other types of oncologic pathology, were treated with noncranial CT and/or RT, and were without such treatment for 5-60 mo. Controls consisted of 15 subjects (5-14 yr old) who were without either pathology or treatment. All patients and controls underwent clinical examination, together with thyroid-stimulating hormone (TSH) T3 and T4 basal tests; the TSH tests were repeated after the subjects were stimulated with thyrotropin-releasing hormone (TRH: 200 ug, iv). Results of the TSH test were within the normal range in the Group A patients; of the Group B patients, six had increased values. The TRH stimulation produced varied results. Twenty-eight of the patients showed changes in thyroid function (TF); most of these were in Group B and represented patients who did not receive cranial RT. The effect of RT, especially CT, on TF should be followed-up. (21 Refs) (In ITA)

15. SIGNIFICANCE OF THYROGLOBULIN AS A TUMOR MARKER IN THE SERUM OF PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA: LONGITUDINAL AND CROSS-SECTIONAL STUDIES.

Schatz H, Grebe S, Maser E, Teuber J, Horn W, Schroder O, Schatz C
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Klin Wochenschr; 60(9):457-464 1982

For evaluating the clinical significance of thyroglobulin measurements for the follow-up of patients with differentiated thyroid carcinoma, thyroglobulin was determined radioimmunologically during the past 2 yr (up to 12x) in 40 patients after withdrawal of thyroid hormone. Thyroglobulin values were compared with whole-body scintigrams after radioiodine. Thyroglobulin antibodies, which may interfere in the radioimmunoassay for thyroglobulin, were also estimated by a radioimmunologic method. In the majority of cases, thyroglobulin levels corresponded to the scintigrams, however, the thyroglobulin level appeared to be a more precise index for changes in tumor tissue mass. In one patient the scintigram was negative, whereas considerable amounts of thyroglobulin were measured in the serum: x-ray tomography revealed a lung metastasis in this case. On the other hand, thyroglobulin was undetectable in the sera of patients who exhibited distinct metastases in the scintigram. Thyroglobulin can be regarded as a tumor marker in patients thyroidectomized for differentiated thyroid carcinoma. However, its determination can certainly not replace whole-body scintigraphy as postulated by several authors, although thyroglobulin measurement appears to be superior to scanning in some cases. A combined application of iodine scanning and thyroglobulin radioimmunoassay is thus advisable in the follow-up of patients with differentiated thyroid carcinoma. (Author abstract) (18 Refs) (In GER)

16. RESULTS OF ORAL TRH TEST IN THE DIFFERENTIATION OF COMPENSATED AND DECOMPENSATED AUTONOMOUS THYROID NODULES.

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Klin Wochenschr; 60(9):477-478 1982

In 17 patients with compensated autonomous adenomas of the thyroid, iv thyrotropin releasing hormone (TRH) tests (200 ug) and oral TRH tests (40 mg) were performed. In nine of these patients, thyroid-stimulating hormone (TSH) 30 min after iv TRH showed a normal (greater than 2.7 uU/ml) and in eight patients a subnormal (less than 2.7 uU/ml) or negative response. However, after prolonged oral stimulation with 40 mg TRH, after 120-180 min TSH was normal (greater than 2.7 uU/ml) in 15 and subnormal (less than 2.7 uU/ml) in 2 patients. In 20 patients with decompensated autonomous thyroid nodules, TSH was not detectable (less than 0.8 uU/ml) after iv or oral TRH stimulation. Therefore, the oral TRH stimulation test seemed to be superior to the iv TRH test in the discrimination of compensated and decompensated autonomous adenomas of the thyroid. (Author abstract) (5 Refs)

17. THYROID FUNCTION AND BREAST CANCER.

Shibusaw K
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Kango; (7):125 1981

A detailed study by the Mayo Clinic on 3,146 patients treated for hyperthyroidism showed no relationship between the frequency of breast cancer to the type of hyperthyroidism, the year and the method of treatment or to the amount of I131 used. However, since the nuclei of human breast cancer cells were found to have receptors for thyroid hormone, the relationship between thyroid and breast cancer should be reinvestigated. (no Refs) (In JPN)

18. THERAPY OF HYPERCALCEMIA DUE TO PARATHYROID CARCINOMA WITH INTRAVENOUS DICHLOROMETHYLENE DIPHOSPHONATE.

Shane E, Jacobs TP, Siris ES, Steinberg SF, Stoddart K, Canfield RE, Bilezikian JP
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Am J Med; 72(6):939-944 1982

Dichloromethylene diphosphonate (Cl2MDP), a potent inhibitor of osteoclast-mediated bone resorption, lowers serum calcium in hypercalcemia associated with malignancies and with primary hyperparathyroidism, and reduces excess calcium mobilization from bone in multiple myeloma and in Paget's disease. We have evaluated the effectiveness of intravenously administered Cl2MDP in five patients with parathyroid carcinoma, a disorder characterized by severe hypercalcemia, very high parathyroid hormone (PTH) levels, and marked osteoclast-mediated bone resorption. All patients had biopsy-proved metastatic parathyroid carcinoma and hypercalcemia which persisted after multiple surgical procedures and other attempts at management. During a 3-day observation period, each patient continued to demonstrate stable or progressive hypercalcemia despite infusion with saline soln and furosemide. Cl2MDP was administered over 2 hr at 2.5 mg/kg on Day 1 and 5 mg/kg on Days 2 through 7. Response was noted in all five patients; there was a gradual decline in the av serum calcium by the 8th day. There were concomitant reductions in urinary calcium excretion, and in the urinary hydroxyproline excretion. Serum PTH levels remained markedly elevated. In three patients, all indices returned to pretreatment levels by 10 days after the last infusion. In two of these patients there was a response to retreatment with Cl2MDP with a fall in calcium from 16.9 +-0.5 mg/dl to 12.4 +-1.5 mg/dl. There was no response in one patient. No adverse reactions to Cl2MDP were observed. The decrease in serum calcium and concomitant declines in urinary calcium and hydroxyproline suggest that Cl2MDP can effectively inhibit the excessive bone resorption associated with parathyroid carcinoma. (18 Refs)

19. IMMUNOREACTIVE SERUM CALCITONIN IN PATIENTS WITH MAMMARY CARCINOMA.

Fereberger W, Leb G, Passath A, Samonigg H, Beaufort F
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MMW; 124(19):471-472 1982

Serum calcitonin levels in 50 women with mammary carcinoma were measured by means of a 125I radioimmunoassay. Twenty healthy men served as controls. Bone metastases were diagnosed in 36/50 women. Elevated levels of calcitonin were found in 6/50 women; these 6 women had varying degrees of disease progression. Levels for the entire group of the patients did not differ significantly from those for the controls. Serum calcitonin is therefore not of value as a tumor marker in patients with mammary carcinoma. (9 Refs) (In GER)

20. CALCITONIN AND CARCINOEMBRYONIC ANTIGEN IN POORLY DIFFERENTIATED FOLLICULAR CARCINOMA.

Calmettes C, Caillou B, Moukhtar MS, Milhaud G, Gerard-Marchant R
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Cancer; 49(11):2342-2348 1982

Previous studies have shown that certain patients suffering from poorly differentiated follicular carcinoma (PDFC) of the thyroid had high levels of calcitonin (CT) and carcinoembryonic antigen (CEA) in the plasma. In this work, both CT and CEA were localized in tissue sections obtained at operation from patients suffering from PDFC. The results confirm the hypothesis that certain cases of PDFC are in fact CT-secreting tumors and represent another type of thyroid neoplasma. Patients suffering from PDFC should be screened using both CT and CEA assays. (Author abstract) (26 Refs)

21. LOW SERUM THYMIC HORMONE LEVELS IN PATIENTS WITH CHRONIC GRAFT-VERSUS-HOST DISEASE.

Atkinson K, Incefy GS, Storb R, Sullivan KM, Iwata T, Dardenne M, Ochs HD, Good RA, Thomas ED
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Blood; 59(5):1073-1077 1982

We tested the hypothesis that chronic graft-versus-host disease (GVHD) is due to inadequate thymic function by examining pretransplant serum levels of facteur thymique serique (FTS). Four of five patients with no detectable FTS activity developed chronic GVHD, while one of four with some FTS activity did. Further patient numbers are needed to confirm or reject this hypothesis. We further postulated that chronic GVHD, whatever its cause, involves thymic epithelium as a target organ. When tested 11 mo or more posttransplant, patients with chronic GVHD had lower absolute FTS levels (p less than 0.02) and lower age-corrected levels ($p = 0.05$) than patients without chronic GVHD. Low values in chronic GVHD were associated with the disease itself and not its therapy. These findings show that thymic epithelial secretory function is impaired in chronic GVHD, and this may in part be responsible for the immunodeficiency characteristic of these patients. (Author abstract) (27 Refs)

22. SUSTAINED SUPPRESSION OF TESTOSTERONE PRODUCTION BY THE LUTEINISING-HORMONE RELEASING-HORMONE AGONIST BUSERELIN IN PATIENTS WITH ADVANCED PROSTATE CARCINOMA. A NEW THERAPEUTIC APPROACH?

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Lancet; 1(8281):1097-1099 1982

Nine patients with advanced carcinoma of the prostate were treated with the luteinizing-hormone-releasing-hormone agonist buserelin (2 mg/day subcutaneously for 3 days then 0.4-1.2 mg/day intranasally for up to 24 wk). There was a rise in luteinizing-hormone levels during the first few days of treatment, but levels fell after 3 wk and remained lower than normal after 24 wk treatment. In patients receiving 0.6-1.2 mg buserelin per day testosterone levels fell to less than 1 ng/ml within 3 wk and were still as low as those found in surgically castrated men after 24 wk. Histology showed regressive changes in some tumors after 3-6 mo buserelin treatment similar to those seen in surgically castrated men. Buserelin treatment may be an alternative to surgery in patients with advanced carcinoma of the prostate. (Author abstract) (13 Refs)

23. THE EFFECTS OF ORCHIDECTOMY, ESTROGENS, AND CYPROTERONE ACETATE ON PLASMA TESTOSTERONE, LH, AND FSH CONCENTRATIONS IN PATIENTS WITH CARCINOMA OF THE PROSTATE.

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Dept. Urology, Univ. Hosp., Linkoping, Sweden
Scand J Urol Nephrol; 16(1):31-36 1982

The peripheral plasma concentrations of testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) were determined in 46 patients (age 51-86 yr) with cytologically confirmed prostatic carcinoma. Treatment consisted of subcapsular orchidectomy (15 cases) or estrogen medication (16 cases) or cyproterone acetate (15 cases). The determinations were made before and 2 wk and 2 mo after treatment was initiated. No correlation was found between the pretreatment levels of testosterone and gonadotrophins and the local extent of the primary tumor or the degree of malignancy. Nor was there any correlation between hormonal level, presence of metastases or patient age. Orchidectomy and estrogen medication both resulted in very low plasma testosterone levels, corresponding to 15% of the pretreatment values. This proportion was 28% in the group treated with cyproterone acetate. Orchidectomy was followed by significant increase in the levels of LH and FSH. Estrogen treatment resulted in suppression of the LH levels to 40% and of FSH to 14% of the pretreatment values. The corresponding decreases in response to cyproterone acetate were 65 and 35%. The results indicate that reduction in gonadotrophin secretion is the primary mechanism in the lowering of testosterone levels produced by treatment with estrogens or cyproterone acetate. (Author abstract) (45 Refs)

24. THE EFFECT OF A POTENT LHRH ANALOGUE IN THE TREATMENT OF PROSTATIC CANCER (MEETING ABSTRACT)

Trachtenberg J, Tolis G

No affiliation given

77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Certain LHRH (luteinizing hormone-releasing hormone) analogues have been shown to markedly reduce gonadal steroidogenesis in a variety of animals. In order to assess to the effect of the chronic administration of a potent LHRH analogue, (D-Ser(But)6)LRH(1-9)-nonapeptide-ethylamide (Hoechst, Hoe766) on prostatic tissue, adult Wistar rats were administered either 1, 3 or 13 ug of Hoe766 sc QD. At 7, 21 and 35 days of treatment, groups of animals were sacrificed and certain serum endocrine and gravimetric parameters determined. By the end of the experimental period neither serum LH nor prolactin was altered from control but serum estradiol, testicular LH receptor content, testicular weight, seminal vesicle weight, and prostate weight were markedly decreased from control; serum androgens were reduced to the castrate level. Hoe766 was also administered to 6 adult males with previously untreated metastatic prostatic cancer. Fifty ug of Hoe766 was administered sc QD or 500 ug intranasally QD for periods from 3 to 6 months. By 3 months of treatment serum prolactin and LH had not changed, but serum androgens and estradiol had declined to the castrate level and LH response to LHRH administration, serum acid phosphatase, and prostatic tumor volume as measured by pelvic ultrasound and bone scan were all markedly reduced. Hoe766 reduces serum androgens to the castrate level in both the rat and man, probably by acting at two sites, namely the pituitary (as evidenced by decreased LH response to LHRH administration) and the testis (as evidenced by decreased testicular LH receptor content). (no Refs)

25. EFFECTS OF TOTAL AND SUBCAPSULAR ORCHIDECTOMY ON SERUM CONCENTRATIONS OF TESTOSTERONE AND PITUITARY HORMONES IN PATIENTS WITH CARCINOMA OF THE PROSTATE.

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Urol Int; 37(2):139-144 1982

Twenty-two men with carcinoma of the prostate were consecutively subjected to either total or subcapsular orchidectomy at random. Serum concentrations of testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, thyroid-stimulating hormone and testosterone-estrogen-binding globulin were followed. No differences were found between the two groups during the 6-mo follow up period. Orchidectomy reduced testosterone concentration in all cases and none responded to human chorionic gonadotrophin stimulation 6 mo postoperatively. The concentrations of free and bound testosterone were calculated but did not vary between the two types of operation, which were considered equally efficient in reducing testosterone concentration. However, doubts about the completeness of the operation might possibly arise in cases with cancer progress and therefore we prefer total orchidectomy as the first choice, but perform subtotal orchidectomy on those men preferring this type of operation psychologically. (Author abstract) (20 Refs)

26. LEUPROLIDE IN METASTATIC PROSTATIC CANCER (MEETING ABSTRACT)

Smith JA

Abbott Leuprolide Prostatic Cancer Study Group, Salt Lake City, UT

77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Leuprolide is a new, potent analogue of gonadotropin releasing hormone which with chronic administration results in inhibition of pituitary release of LH and FSH (luteinizing and follicle stimulating hormones). Consequently testicular function is suppressed in men and circulating serum testosterone levels reduced. These observed endocrine effects of Leuprolide have predicated its use in prostatic cancer. One hundred and seventeen patients with metastatic prostatic cancer have been treated with Leuprolide in a multi-center Phase I-II study. Fifty-seven patients had received some form of prior endocrine treatment and 60 had no prior therapy. Patients were followed every two weeks and serial bone scans, x-rays and serum chemistries and hormones obtained according to protocol. Response criteria were those defined by the National Prostatic Cancer Project. Serum testosterone and dihydrotestosterone were suppressed to castrate levels in all patients within four weeks of the initiation of treatment. No adverse reactions or gynecomastia were encountered in any patients although most had hot flashes. Thirty previously untreated patients are evaluable to date and 70% have obtained a complete or partial objective response. An additional 27% have objectively stable disease and most patients had subjective improvement with resolution of bone pain or improvement in performance status. All responding patients are continuing on treatment. Only one patient in the previously untreated category had disease progression at week 10 of treatment. Thirty percent of patients who had relapsed on prior endocrine treatment had some subjective improvement with Leuprolide and 2 achieved an objective response. (no Refs)

27. GONADAL FUNCTION AFTER CHEMOTHERAPY IN TESTICULAR CANCER PATIENTS (MEETING ABSTRACT)

Donohue JP, Drasga RE, Williams SD, Einhorn LH, Patel DN, Stevens EE

No affiliation given

77th Annual Meeting of the American Urological Association, Inc., may 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Evaluation with sperm counts, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone were performed retrospectively on 17 stage C testis cancer patients who did not have a retroperitoneal lymphadenectomy (RPLND). These patients were treated with platinum, vinblastine, bleomycin (PVB) with or without doxorubicin between 1975 to 1979. The median follow-up initiation of chemotherapy is 3 years. Of 15 patients, 7 had sperm counts above 20 x 10(6)/ml. FSH levels were normal in 9 of 17. LH levels were normal in 11 of 17 and testosterone values were normal in 13 of 17. There have been 3 healthy babies born and there is one ongoing pregnancy. Starting in 1979, a prospective study was undertaken in stage B3 or C testis cancer patients. These patients had no prior RPLND and were treated with PVB with or without doxorubicin. To date 36 patients have been entered. Pretreatment only 6 of 26 had sperm counts above 20 x 10(6)/ml. Elevated FSH levels were found in 1 of 36 pretreatment. After 9 weeks of chemotherapy, 18 of 18 were oligospermic and 17 of 18 were aspermic. Of 28 patients, 16 had elevated FSH levels at 9 weeks. At 1 year from the start of therapy, 6 of 7 remain aspermic and 12 of 13 have elevated FSH levels. There has been 1 healthy baby born and 1 ongoing pregnancy in this group. (no Refs)

28. GONADOTROPH CELL ADENOMAS OF THE HUMAN PITUITARY (MEETING ABSTRACT)

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Lab Invest; 46(1):37A 1982

Hypersecretion of gonadotrophins causes no conspicuous clinical symptoms, hence patients with FSH- (follicle stimulating hormone) and LH- (luteinizing hormone) producing adenomas are often claimed to have non-functioning adenohypophysial tumors. The diagnosis can also be missed by pathologic examination, since morphologic features of adenomas arising in gonadotrophs are insufficiently explored. In our material of 495 surgically removed pituitary adenomas, six were identified by the immunoperoxidase technique as gonadotrophin-containing tumors. They were chromophobic with fine periodic acid-Schiff-positive granulation; FSH was demonstrated in two, LH in one, FSH and LH in three tumors, indicating that both gonadotrophins can be produced in the same adenoma cell. Three adenomas occurred in men, three in women; the disease was suspected in two men with elevated blood FSH; one woman had long-standing primary hypogonadism. Electron microscopy revealed that the adenoma cells were undifferentiated and differed from nontumorous gonadotrophs in men; whereas they appeared more differentiated in women and, similar to nontumorous gonadotrophs, contained prominent, dilated Golgi complexes and rough endoplasmic reticulum membranes. Five additional tumors removed from women resembled the three female cases in ultrastructure, suggesting that they too originated in gonadotrophs, but because of negative immunostaining this remained conjectural. (no Refs)

29. PITUITARY ADENOMAS: AN IMMUNOCYTOCHEMICAL STUDY OF 147 TUMORS IN 140 PATIENTS (MEETING ABSTRACT)

Mukai K
Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN
Lab Invest; 46(1):59A 1982

Immunocytochemical study of prolactin (Prl), growth hormone (GH), ACTH, gonadotropins (LH/FSH (luteinizing hormone/follicle stimulating hormone)), and TSH (thyroid stimulating hormone) was performed in 147 pituitary adenomas from 140 patients (male:female 3:4; 13 to 81 years old), and the results were correlated with the clinical manifestations. Eighty-six tumors were positive for one hormone, eight tumors for two hormones, and 53 tumors were negative for all hormones tested. In the first group, there were 40 Prl-positive tumors in females (amenorrhea-galactorrhea, 30; amenorrhea, seven; hirsutism, one; delayed puberty, one; and hypopituitarism, one); 19 Prl-positive tumors in males (hypogonadism, five; galactorrhea, two; gynecomastia, two; delayed puberty, one; growth retardation, one; and no specific endocrine symptoms, eight); 12 GH-positive tumors (acromegaly, 11; and amenorrhea-galactorrhea, one); nine ACTH-positive tumors (Cushing's syndrome, seven; Nelson's syndrome, one; and hirsutism, one); and six LH/FSH-positive tumors (no specific endocrine symptoms, six). The second group consisted of six Prl- and GH-positive tumors (acromegaly, six); one Prl- and ACTH-positive tumor (amenorrhea-galactorrhea, one) and one Prl- and TSH-positive tumor (no specific endocrine symptoms, one). The third group was comprised of 53 tumors without hormone production by immunocytochemistry (amenorrhea-galactorrhea, three; amenorrhea, two; growth retardation, one; and no specific endocrine symptoms, 47). (no Refs)

30. DIAGNOSIS OF PITUITARY TUMORS BY HORMONE ASSAYS AND COMPUTERIZED TOMOGRAPHY.

Valenta LJ, Sostrin RD, Eisenberg H, Tamkin JA, Elias AN
Diabetes and Endocrine Clinic of North County, 2131 El Camino Real, Oceanside, CA, 92054
Am J Med; 72(6):861-873 1982

One hundred and seventy patients with endocrine abnormalities, 29 males and 141 females, were studied by computerized tomography (CT) scanning of the pituitary and by pituitary hormone assays including basal and stimulated hormone concentrations in the blood. Pituitary macroadenoma was observed in 40 of the 170 patients, microadenoma in 49, primary empty sella in 46, secondary empty sella in 25, including 20 of the 40 patients with macroadenoma after surgical removal or radiation therapy of the tumor. Suprasellar tumor was present in four patients. In 23 women with menstrual abnormalities and 3 men with impotence and hyperprolactinemia, the results of CT scanning were normal. Of the 40 patients with macroadenoma, 24 presented with a hyperfunctioning syndrome (acromegaly or hyperprolactinemia). Among the 49 patients with microadenomas, 46 had the amenorrhea-galactorrhea syndrome, one male presented with acromegaly and one with Cushing's disease, and one female also had Cushing's disease. Primary empty sella was associated with the amenorrhea-galactorrhea syndrome in females and impotence in males. Only four female patients demonstrating an empty sella were asymptomatic. Distinctive biochemical findings were identified in certain groups of patients with different pituitary pathologic features. CT scanning was found very useful in the assessment of the size of the tumor, its suprasellar or parasellar extension and response to therapy, and in differential diagnosis of tumor and empty sella. Disappointing results were obtained in patients with endocrine abnormalities and normal results of CT scanning, and in patients following surgical treatment for a pituitary tumor, when the identification of recurrent tumor was impossible for a single examination. It is concluded that CT scanning is the most advanced technique in the diagnosis of anatomic pituitary abnormalities, and it should replace the traditional invasive diagnostic procedures. (Author abstract) (21 Refs)

31. EFFECT OF HYPOTHALAMIC AND PITUITARY IRRADIATION ON PUBERTAL DEVELOPMENT IN CHILDREN WITH CRANIAL TUMORS.

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J Clin Endocrinol Metab; 54(6):1164-1168 1982

The purpose of the present study was to report on gonadotropin function and puberty of a large group of children treated by cranial irradiation for cranial and neck tumors and medulloblastoma. Forty-five children of pubertal age were investigated. The mean interval time since radiation was 5 2/12 yr. Gonadotropin and gonadal function were evaluated by clinical criteria, plasma sex steroids, and plasma LH and FSH responses to LRH. Puberty was complete or progressing normally in 31 cases and was abnormal in 14 cases. Severe gonadotropin deficiency, with lack of or slow progression of puberty and decreased LH and FSH responsiveness to LRH, was observed in five cases; two of these had moderately elevated plasma

PRL levels. Secondary amenorrhea or lack of pubertal progression was found in five other cases. GH deficiency was associated with gonadotropin deficiency in 9 of these 10 cases. Adrenal function, estimated by basal dehydroisoepiandrosterone, dehydroisoepiandrosterone sulfate, and estrone, was normal according to pubic hair stages. In conclusion, complete or partial gonadotropin deficiency can be the consequence of cranial irradiation in children receiving 6,000 rads or less. It is usually associated with GH deficiency. The site of the damage on the pituitary gland or the hypothalamus remains to be demonstrated. (Author abstract) (22 Refs)

32. SELLA 'EROSIONS' IN A SERIES OF 50 NORMAL WOMEN: THE PLACE OF TOMOGRAPHY IN THE DIAGNOSIS OF PROLACTIN SECRETING PITUITARY MICROADENOMA.

Weinstein D, Rothman SL, Geehr RB, Siew F, Klepfish A, Schenker JG

Dept. Obstetrics and Gynecology, Hadassah Medical Sch., Jerusalem, Israel

Eur J Obstet Gynecol Reprod Biol; 13(3):169-175 1982

Results of hypocycloidal tomography of the sella in 50 women (aged 23-40 yr) with normal pituitary and reproductive function were examined. All films were reviewed independently by four neuroradiologists with major interest in the pituitary fossa. Sella tomograms were uniformly read as normal in only 16 of the 50 cases. In 14 cases all four observers read the tomograms as showing objective evidence of intrasellar microadenoma. In the remaining cases, the observers were divided as to normality of the tomograms. All abnormalities were interpreted as indicating an expanding intrasellar mass. Three representative case histories are presented. Results emphasize the need for caution in interpreting the tomographic diagnosis of pituitary microadenoma, since clear guidelines for evaluating sellar changes have not been established. (21 Refs)

33. NOMIFENSINE TEST DOES NOT DIFFERENTIATE HYPERPROLACTINEMIA ASSOCIATED WITH AND WITHOUT RADIOLOGIC ABNORMALITIES IN THE SELLA TURCICA.

Canales ES, Cano C, Ablanedo J, Zarate A

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Horm Res; 15(4):213-217 1981

A group of 17 hyperprolactinemic women was given 200 mg of nomifensine orally to evaluate its diagnostic potential to discriminate between tumors and nontumorous hyperprolactinemia. The nomifensine suppressive effect on prolactin serum levels was not significantly different between patients with or without enlargement of the sella turcica. A control group of five women with normal prolactin levels exhibited a nomifensine suppressive effect below 65% of the baseline prolactin level, which was significantly different from that in the hyperprolactinemic group. In conclusion it is confirmed that the nomifensine test provides no value in the early diagnosis of the prolactinoma. (Author abstract) (7 Refs)

34. ORAL CONTRACEPTIVES AND PROLACTINOMAS: A CASE-CONTROL STUDY.

Maheux R, Jenicek M, Cleroux R, Beauregard H, De Muylder X, Gratton NM, Van Campenhout J

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Am J Obstet Gynecol; 143(2):134-138 1982

The increase in the number of newly diagnosed cases of prolactinomas seems to coincide with the use of oral contraceptives during the past 2 decades. The following retrospective case-control study was undertaken in an attempt to disprove a null hypothesis of relationship between oral contraceptive use and prolactinomas. Each of 70 patients operated upon for removal of a prolactinoma was closely matched for age, gravidity, and year of final diagnosis with one patient in each of three control groups. The control groups selected were constituted, respectively, of patients with secondary amenorrhea and normal prolactin levels, patients with normal ovulatory cycles consulting for infertility, and subjects without medical or gynecologic problems. No statistically significant differences were found in the exposure rates to oral contraceptives among the four groups. This study thus failed to reveal a significant association between prolactinomas and oral contraceptives but, given the sample size, a relative risk lower than 3.32 cannot be demonstrated or disproved. (Author abstract) (23 Refs)

35. THE AUTONOMY OF PROLACTIN SECRETION IN PATIENTS WITH PROLACTIN PRODUCING TUMOR.

Hanew K, Sasaki A, Sato S, Murata K, Fukui M, Koh K, Shimizu Y, Murakami O, Yoshinaga K

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Tohoku J Exp Med; 137(1):101-107 1982

To evaluate possible differences in autonomy of prolactin secretion in prolactin producing tumors, TRH, arginine, sulpiride, and L-dopa were administered to 13 patients with prolactin secreting tumors and plasma prolactin responses were determined. All 13 patients were administered TRH, arginine, and sulpiride. Seven cases showed an increase in prolactin in excess of 50% of the basal value in response to TRH, three demonstrated an increase in response to arginine, and four showed an increase in response to sulpiride. Seven of these cases showed responses to at least TRH, or to TRH and other stimuli. The remaining six cases showed no response to any of the stimuli. No correlations were observed between sellar volumes and mean basal values of prolactin in any of the patients. After 500 mg L-dopa ingestion, TRH responders showed a prompt decrease in prolactin from 30 min and reached a nadir at 150 min. Non-responders showed some decrease in prolactin after L-dopa ingestion, but these were not as dramatic as those observed for TRH responders. (30 Refs)

36. THE FOOD-ENTRAINED PROLACTIN AND CORTISOL RELEASE IN LATE PREGNANCY AND PROLACTINOMA PATIENTS.

Quigley ME, Ishizuka B, Ropert JF, Yen SS

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J Clin Endocrinol Metab; 54(6):1109-1112 1982

Abrupt and concomitant increments in circulating cortisol and PRL levels in association with food intake at noon were observed in hyperprolactinemic pregnant women. During late pregnancy, the quantitative release was at least 12-fold greater for PRL and substantially more for cortisol compared to values in nonpregnant women. In contrast, patients with hyperprolactinemia due to prolactinoma exhibited an absence of the PRL response to the noon meal and a significantly smaller rise in cortisol, suggesting an independent mechanism for the release of these two hormones due to food ingestion. These observations may be important for future elucidation of neuroendocrine links between feeding and metabolic homeostasis in pregnancy. (Author abstract) (35 Refs)

37. ELEVATED INTRAVESICULAR FLUID LUTEINIZING HORMONE CONCENTRATION IN HYDATIDIFORM MOLE.

Gunasegaram R, Peh KL, Loganath A, Karim SM, Ratnam SS
Dept. Pathology, Singapore General Hosp., Singapore 0316, Singapore
Br J Obstet Gynaecol; 89(2):160-162 1982

Concentrations of human chorionic gonadotrophin (beta-hCG), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL) were measured by radioimmunoassay in the serous fluid of hydatid vesicles obtained from 27 patients with hydatidiform mole. High amounts of all four hormones were found in every case. The mean concentrations +-SEM were 710.8 +-100.8 iu/l x 10(-3) for beta-hCG, 13.8 +-0.3 iu/l for FSH, 302.2 +-34.5 iu/l x 10(-3) for LH and 2,610.8 +-562.1 m-iu/l for PRL. It is suggested that aberrations in the mechanisms controlling the synthesis and release of luteinizing hormone-releasing factor (LH-RF) could result in chronically elevated LH levels leading to changes characteristic of this disease. (Author abstract) (8 Refs)

38. DECREASED NOCTURNAL PLASMA MELATONIN PEAK IN PATIENTS WITH ESTROGEN RECEPTOR POSITIVE BREAST CANCER.

Tamarkin L, Danforth D, Lichter A, DeMoss E, Cohen M, Chabner B, Lippman M
NIH, Building 6, Room 136, Bethesda, MD, 20205
Science; 216(4549):1003-1005 1982

Plasma melatonin concentrations were determined over a period of 24 hr in 20 women with clinical Stage I or II breast cancer. In 10 of the patients, whose tumors were estrogen receptor positive, the nocturnal increase in plasma melatonin was much lower than that observed in 8 control subjects. Women with the lowest peak concentration of melatonin had tumors with the highest concentrations of estrogen receptors. A significant correlation was found between the peak plasma melatonin concentration and the tumor estrogen receptor concentration in 19 of the patients. These data suggest that low nocturnal melatonin concentrations may indicate the presence of estrogen receptor positive breast cancer and could conceivably have etiologic significance. (Author abstract) (18 Refs)

39. TREATMENT WITH A LUTEINISING-HORMONE-RELEASING-HORMONE ANALOGUE (BUSERELIN) IN PREMENOPAUSAL PATIENTS WITH METASTATIC BREAST CANCER.

Klijn JG, DeJong FH
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Lancet; 1(8283):1213-1216 1982

Four premenopausal women with metastatic breast cancer were treated with a potent luteinizing-hormone-releasing-hormone (LHRH) analogue as a single first-line agent. Buserelin (6-D-ser-(bu1)-LHRH-(1-9)-ethylamide) was given in very high doses intravenously and then intranasally; ovarian function did not decrease within 1-2 wk, but after this period low to very low (postmenopausal) plasma estradiol levels were reached in all patients, accompanied by flushes. Two patients, however, subsequently showed transient peaks of plasma estradiol, probably due to a persistent follicle, which lasted for some wk without a rise in plasma luteinizing hormone, follicle-stimulating hormone, or progesterone. In two patients there was no significant change in the tumor, whereas in the other two patients there was remarkable improvement. (Author abstract) (22 Refs)

40. CURRENT VIEWS ON HORMONES AND BREAST CANCER.

Molinatti GM, Limone P
Cattedra di Endocrinologia, Universita di Torino, C.so Polonia, 14, 10126 Turin, Italy
Minerva Med; 73(17):1047-1053 1982

Recent studies on relationships between hormone status and breast cancer in women are reviewed. The pathophysiological aspects of estrogens, prolactin, dehydroepiandrosterone and dehydroepiandrosterone sulfate and therapeutic significance of estrogen and prolactin receptors are discussed. (57 Refs) (In ITA)

41. THE ROLE OF ESTROGENS IN MASTOPATHY AND MAMMARY CANCER IN PERIMENOPAUSAL WOMEN.

Greenblatt RB, Vasquez J, Samaras C, Nezhat C
Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA, 30901
J Am Geriatr Soc; 30(3):165-169 1982

Fibrocystic disease of the breast (FCD) is an exaggeration of the normal physiologic response to cyclic estrogen and progesterone stimulation. The disorder can persist, with much less severity, in the menopausal woman. Whether FCD predisposes to mammary cancer remains moot. A new steroidal agent, danazol, can eliminate nodosities in the majority of women with FCD. Thermography may identify women who are at greater risk because of increased heat production. Mammography should be employed in women with persistently abnormal thermograms, even though no suggestive breast masses are palpable. Needle biopsy or surgical biopsy should be undertaken whenever a firm indurated mass is palpated, regardless of negative findings with a thermogram or mammogram. In a series of 1,548 women treated for 10,715 women-years, the incidence of breast cancer after prolonged estrogen therapy was not increased. Although estrogens and prolactin have been incriminated in the etiology of mammary cancer, no hard facts exist to confirm such allegations. (Author abstract) (34 Refs)

42. ENDOCRINOLOGICAL EFFECTS OF MEDROXYPROGESTERONE ACETATE IN HUMANS (MEETING ABSTRACT)

Jannotta SG, Facchinetti A
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International Symposium on Medroxyprogesterone Acetate, February 24-26, 1982, Geneva, Switzerland. Farmatalia Carlo Erba 91 pp., 1982.

In order to correlate the endocrine properties of MPA (medroxyprogesterone acetate) with its serum concentrations after intramuscular or oral administration of high doses (0.5-1-2 g/day), the behavior of gonadal, adrenal, prolactin and GH (growth hormone) functions were studied in humans under different experimental conditions. Antiestrogenic and antiandrogenic activity of MPA were represented by the reduction in plasma estradiol and testosterone. In addition, plasma FSH (follicle stimulating hormone) and LH (luteinizing hormone) were decreased by 0.5 g MPA im/day for 30 days or 1 g only by treatment for 1 month at the high doses. Basal prolactin and GH, and their increase after TRH (thyrotropin-releasing hormone) and arginine stimulation, were not modified by MPA therapy. MPA inhibited the adrenal gland, but at the same time presented corticoid-like properties. This phenomenon probably depends upon the formation of one or more MPA metabolites which increase urinary corticoids; MI has been identified as the inactive metabolite of MPA with a dihydroxyacetonic side chain at C-17. (no Refs)

43. HIGH (H) VERSUS LOW (L)-DOSE MEDROXYPROGESTERONE ACETATE (MPA) IN ADVANCED BREAST CANCER (MEETING ABSTRACT)

Cavalli F, Goldhirsch A, Kaplan E, Alberto P
Swiss Group for Clinical Cancer Research, 1205 Geneva, Switzerland
International Symposium on Medroxyprogesterone Acetate, February 24-26, 1982, Geneva, Switzerland. Farmatalia Carlo Erba 91 pp., 1982.

H dose-MPA was recently reported to yield an impressive response rate (RR) in the treatment (Rx) of advanced breast cancer. Therefore 165 postmenopausal patients (pts) with a measurable advanced breast cancer (20% without prior Rx) were randomized between 1000 mg/daily (H) and 500 mg twice weekly (L) MPA im for 4 weeks; responding pts were continued on 500 mg MPA im once weekly. During Rx MPA blood levels were determined every 2-4 weeks in 9 pts (5 H, 4 L). MPA blood levels were consistently and at least twofold higher in pts treated with H, with steady-state levels reached after 4 weeks. Preliminary results of the hormonal determinations show a significant decrease of FSH/LH (follicle stimulating hormone/luteinizing hormone) and a marginal increase of PRL (prolactin) during Rx, without clear correlation with H or L dose. At the last cut-off (2/81) 127 pts were already evaluable. Clinical prognostic factors were well-balanced between H and L. Hormone receptors were known only in 1/3 of pts. Partial response (PR) was observed in 20/65 (30%) pts with H MPA and 7/62 (11%) in L MPA. The more pronounced difference in RR was found in pts refractory to prior Rx (PR: 12/57 in H, 0/53 in L) or with osseous mets (metastasis). (PR: 8/20 in H, 1/19 in L). Median duration of PR was 230+ d in H and 150+ d in L. No Change for a median duration of 128 d was observed in 28 pts: 14 in H, 14 in L. (no Refs)

44. ORAL HIGH-DOSE MPA THERAPY IN ADVANCED BREAST CANCER: CLINICAL AND ENDOCRINE STUDIES (MEETING ABSTRACT)

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Department of Surgery, Gunma University, Maebashi, Japan
International Symposium on Medroxyprogesterone Acetate, February 24-26, 1982, Geneva, Switzerland. Farmatalia Carlo Erba 91 pp., 1982.

Instead of im injection of high-dose MPA (medroxyprogesterone acetate) which sometimes causes local side effects, we have attempted to administer it orally. The clinical effects of MPA given orally at daily doses of 600-2400 mg were studied in 109 patients with advanced breast cancer by a study group in Japan (6 institutions). Overall response rate was 29.3%. In 600-1000 mg group the rate was 14.6% (6/41), in 1200 mg group 38.2% (26/55) and in 1600 or more group 28.6% (2/7), respectively. Some side effects or abnormal laboratory data were seen but most of them were tolerable. Secondly, in the patients at the author's own institution, blood level of MPA and hormones as to pituitary-adreno-ovarian axis were investigated. Blood level of MPA was maintained at least over 50 ng/ml at 1 or 2 months of the therapy. As for hormonal changes, inhibitory effects on plasma LH, FSH (luteinizing, follicle stimulating hormones), ACTH and cortisol were observed. Plasma PRL, GH and TSH (prolactin, growth and thyroid stimulating hormones) showed no marked change. Urinary excretion of 17 OHCS (hydrocorticosteroid) and 17 KS (Ketosteroid) were increased. (no Refs)

45. OPPORTUNISTIC INFECTIONS IN PATIENTS WITH ECTOPIC ACTH-SECRETING TUMORS.

Higgins TL, Calabrese LH, Sheeler LR
Dept. Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, OH
Cleve Clin Q; 49(1):43-49 1982

Laboratory values of 21 patients with Cushing's syndrome are summarized, with values given for plasma ACTH, serum cortisol, urinary cortisol and 17-hydroxy steroids. Case reports of two patients with ectopic ACTH are presented; both patients died due to infection (Aspergillus fumigatus, Nocardia asteroides). Patients with ACTH secreting tumors apparently have altered host defense due to increased cortisol; there is also a dose-dependent effect of corticosteroids on immunosuppression. (21 Refs)

46. PREDICTING SPLENIC ABNORMALITY IN HODGKIN DISEASE USING VOLUME RESPONSE TO EPINEPHRINE ADMINISTRATION.

Rosen PR, Lasher JC, Weiland FL, Kopp DT
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Radiology; 143(3):627-629 1982

The change in relative splenic vol following epinephrine administration was used to determine splenic abnormality noninvasively. Selective splenic imaging was accomplished with 99mTc-labeled heat-treated red blood cells, an LFOV gamma camera, a 30 degree bilateral rotating slant hole collimator, and bilateral slant hole tomographic software. Relative splenic vol were plotted over time, and correlated with clinical and histologic data. Eight patients with Hodgkin disease and other lymphomas were examined. Vol response to epinephrine appears to be significantly less in abnormal spleens, and may serve to identify patients with unequivocally normal spleens prior to treatment. (Author abstract) (15 Refs)

47. THE HEMODYNAMIC RELEVANCE OF FREE AND CONJUGATED DOPAMINE IN PHEOCHROMOCYTOMA.

Kuchel O, Buu NT, Bourque M, Hamet P, Larochelle P
Clinical Res. Inst., 110 Pine Ave. West, Montreal, Quebec H2W 1R7, Canada
J Clin Endocrinol Metab; 54(6):1268-1270 1982

Two patients with adrenomedullary hypersecretion (confirmed pheochromocytoma and adrenomedullary hyperplasia) presented 15 spontaneous crisis associated with hypertension or hypotension with or without tachycardia. Correlation coefficients calculated between extreme values of pulse rates and of systolic and diastolic blood pressures on the one hand and plasma free and conjugated norepinephrine, epinephrine, and dopamine (DA) sampled at the height of the crisis on the other, showed no relationships between free or conjugated norepinephrine or epinephrine and blood pressure or pulse rate. However, plasma conjugated DA was negatively correlated with systolic blood pressures (p less than 0.02) and diastolic blood pressures (p less than 0.03) and free plasma DA was negatively correlated with pulse rates (p less than 0.001). These data suggest that the extremely high circulating level of conjugated DA in pheochromocytoma may, in the presence of high circulating conjugated norepinephrine and possibly high alpha-adrenergic receptor occupancy, decrease blood pressure by its predominant action on dopaminergic receptors while elevated free DA may decrease the tendency to tachycardia, possibly by lowering the venous return. (Author abstract) (12 Refs)

48. A STUDY OF THE HORMONAL CONTENT OF BENIGN AND MALIGNANT PANCREATIC AND DUODENAL ENDOCRINE TUMORS USING THE IMMUNOPEROXIDASE TECHNIC (MEETING ABSTRACT)

Alport EC, Li CY, Carney JA
Department of Surgical Pathology, Mayo Clinic, Rochester, MN, 55901
Am J Clin Pathol; 77(2):245 1982

It is generally recognized that prediction of the biologic potential of certain endocrine tumors, including those of the pancreas and duodenum, is difficult. Sporadic case reports have suggested that endocrine tumors secreting ectopic or multiple hormones are malignant. As a test of this notion, immunoperoxidase methods, standardized for insulin, gastrin, glycagon, somatostatin, serotonin, calcitonin, and ACTH, were used to determine the hormonal content of 26 pancreatic and duodenal endocrine tumors; the type and number of hormones present were correlated with the clinical behavior of the neoplasms. The tumors, surgically obtained between 1956 and 1974, were fixed in buffered formalin and processed routinely for light microscopy. The study included 26 patients, 13 females and 13 males (age: 24-71 yr), nine and 17 of whom had clinical and biochemical findings consistent with insulin- and gastrin-producing tumors, respectively. Fifteen tumors were malignant, all with documented metastasis, and five of these contained more than one hormone. Only one of the 11 benign tumors contained more than one hormone (most cells stained for insulin, a minority for gastrin). Five tumors containing either somatostatin or serotinin were malignant. The results indicate that detection of multiple hormones in pancreatic and duodenal endocrine tumors may be of prognostic value. (no Refs)

49. INSULINOMA: STATISTICS, ESTABLISHED PHYSIOLOGICAL MECHANISMS, AND POLICY.

Ishii H, Nagata S, Mikami F, Takahashi H
Dept. Internal Medicine, Keio Jikei Univ. Sch. Medicine, Tokyo, Japan
Nippon Rinsho; 40(2):434-440 1982

Statistics on Japanese patients with insulinoma show that the patients were 4-85 yr old, 60% of the patients were 30-60 yr old, and the male:female ratio was 1:1.2. Primary clinical symptoms of insulinoma due primarily to conditions of on high blood insulin level and hypoglycemia, are mental confusion in the early morning prior to eating, convulsions, double vision, delirium and hallucination profuse sweating, and weakness. Insulinomas in Japanese patients are located most often in the pancreatic tail and least often in the pancreatic head. Most insulinomas are less than 2 cm in diameter, and 13% of insulinomas in Japan are malignant. Based on data concerning characteristics of the basic hormones involved in insulinoma, abnormal responses of stimulatory hormones, and experimental research on suppression of insulin hormones, a treatment policy was suggested. Surgery is not possible in cases of malignant insulinoma when there is localized lymph node or hepatic metastasis. Many of the malignant insulinoma patients also have hypoglycemia in spite of glucose drip infusion; in these cases, anticancer agents are administered in combination with insulin antagonists. (36 Refs) (In JPN)

50. PLASMA INSULIN RESPONSE TO VARIOUS SECRETAGOGUES IN INSULINOMA.

Ohneda A, Kobayashi T, Nihei J
Third Dept. Internal Medicine, Tokoku Univ. Sch. Medicine, Sendai 980, Japan
Tohoku J Exp Med; 136(4):447-457 1982

It is reported that frequent measurements of plasma insulin during fasting and of insulin/glucose ratios are the most useful parameters for diagnosing insulinoma. Tolbutamide IV revealed an exaggerated insulin response in patients with insulinoma. The glucagon test was found to be useful in delineating patients with insulinoma from those with other hypoglycemic conditions. The combined use of these tests is suggested when insulinoma is included in the differential diagnosis. (31 Refs)

51. FUNCTIONING TUMORS OF THE GUT.

Friesen SR, Petelin JB
Univ. Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, KS, 66103
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

History, diagnosis, pathology, treatment, and prognosis of hormone-producing tumors of the gut are reviewed. Entopic syndromes include carcinoid, glucagonoma, insulinoma, somatostatinoma, and pancreatic polypeptide syndromes. Ectopic syndromes include gastrinoma, vipoma, corticotrophinoma, and parathyrinoma syndromes. (119 Refs)

52. NEUROENDOCRINE PRODUCTS OF INTESTINAL CARCINOIDS: AN IMMUNOPEROXIDASE STUDY OF THIRTY-FIVE CARCINOIDS STAINED FOR SEROTONIN AND EIGHT POLYPEPTIDE HORMONES (MEETING ABSTRACT)

Yang K, Ulich TR, Cheng L, Lewin KJ
Department of Pathology, University of California at Los Angeles, Los Angeles, CA
Lab Invest; 46(1):91A 1982

The purpose of this study was to determine the distribution of neuroendocrine products within intestinal carcinoids, their metastases, and the epithelium overlying the tumors. Thirty-five intestinal carcinoid tumors from 26 patients were stained for the presence of serotonin, gastrin, somatostatin, motilin, secretin, glucagon, ACTH, neurotensin, and pancreatic polypeptide carboxyl-terminal hexapeptide-like material. Argentaffin and argyrophil stains were also performed. Serotonin was present in 30 of the 35 tumors. Nineteen tumors contained serotonin only. Fourteen cases contained multiple neuroendocrine products including up to five polypeptide hormones. One tumor contained gastrin only. One tumor did not stain immunohistochemically but was argyrophilic. In some cases, metastatic deposits produced the identical neuroendocrine products as the primary tumor, whereas others produced either additional or fewer hormones than the primary tumor. Argyrophilic cells were present in all cases and were much more numerous than cells stained by immunohistochemistry. Argyrophilic cells probably contain monoamines and polypeptide hormones in addition to those studied in this series. The carcinoid syndrome, as clinically defined by the presence of flushing and diarrhea, was noted in five patients, all of whom had serotonin-containing small bowel carcinoids. Endocrine-related symptoms were not clinically appreciated in the remaining patients. (no Refs)

53. GLUCAGONOMA AND SOMATOSTATINOMA.

Yoshida H, Shimizu N
First Dept. Internal Medicine, Teikyo Univ. Sch. Medicine, Kanagawa Prefecture, Japan
Nippon Rinsho; 40(2):441-445 1982

Clinical patterns of glucagonoma and somatostatinoma are discussed, and a case of glucagonoma is reported. Glucagonomas occur most often in patients 50-80 yr old, and metastases are common. Careful determination of the mol wt of the glucagon is essential in characterizing the disease. Important clinical symptoms observed in the patient with somatostatinoma included diabetes, insufficient emptying of the gall bladder, gallstones, and constipation. (28 Refs) (In JPN)

54. CHANGES IN THE DIAGNOSIS AND TREATMENT OF ZOLLINGER-ELLISON SYNDROME.

Feurle GE, Helmstadter V, Hoevels J, Wenzel-Herzer G, Klempa I
Medizinische Universitats-Poliklinik, Hospitalstr. 3, 6900 Heidelberg 1, W. Germany
Dtsch Med Wochenschr; 107(18):697-704 1982

A gastrinoma was found in 12 of 23 patients with Zollinger-Ellison syndrome. Those with gastrinoma were not different from those without as regarded fasting gastrin level, increased gastrin secretion after secretin and calcium, acid secretion, or survival time. Five of the 23 patients have died, 4 immediately postoperatively, the 5th of the metastasizing tumor. Treatment with the H2-receptor antagonist cimetidine avoided emergency operation and thus decreased operative mortality, giving time for localization by ultrasound, computed tomography and selective arteriography. The rate of false-negative results was high. Transhepatic selective catheterization of the pancreatic veins with gastrin determination gives localization of the tumor and identification of the secreted hormone. In three patients tumor resection was possible under cover of H2-receptor antagonist administration which normalized gastrin and acid secretion. There is a change in the treatment of the Zollinger-Ellison syndrome, away from total gastrectomy to conservative treatment with H2-receptor antagonists and an attempt of curative treatment by removal of the tumor. (Author abstract) (39 Refs) (In GER)

55. IMMUNOCYTOCHEMICAL ANALYSIS OF GASTRIC ADENOCARCINOMAS FOR CREATINE KINEASE B POLYPEPTIDE AND SEROTONIN (MEETING ABSTRACT)

Miller SA, Li CY, Homburger HA
Mayo Clinic, Rochester, MN, 55901
Am J Clin Pathol; 77(2):245 1982

In a previous study, we identified both the B polypeptide of creatine kinase (CK-B) and serotonin (SER) by an immunoperoxidase technic (IPT) in neoplastic cells from one of four gastric adenocarcinomas (G-ADCA). To evaluate the frequency and prognostic significance of positive staining for CK-B and SER in G-ADCA, we studied tumors from 30 patients with surgically resected G-ADCA, 17 of whom survived at least 5 years. CK-B was demonstrable in formalin fixed tumors from 10 cases; six of whom survived at least 5 years. Only two tumors stained strongly for CK-B, and each patient survived at least 5 years despite full-thickness infiltration of the gastric wall and regional lymph node metastases at the time of surgery. SER was demonstrable in eight tumors; seven were of the signet cell type, and two also contained CK-B. Survival was not enhanced in patients with SER positive tumors. We conclude that the neoplastic cells of G-ADCA frequently synthesize either CK-B or SER. Large amounts of CK-B, demonstrable by IPT in neoplastic cells, may be an independent indicator of a favorable prognosis in G-ADCA; and, in such cases, CK-B in serum may be a useful indicator of recurrent carcinoma. (no Refs)

56. EFFECT OF COMBINED TREATMENT WITH PREOPERATIVE GAMMA THERAPY ON FUNCTIONAL STATE OF GASTRIN-PRODUCING CELLS IN PATIENTS WITH STOMACH CANCER.

Berdov BA, Vedzizheva TB, Bassalyk LS, Zagrebin VM
Res. Inst. Medical Radiology, Obninsk, USSR
Med Radiol (Mosk); 27(4):20-24 1982

Functional activity of gastrin-producing cells (G cells) was studied in 160 patients (103 men, 57 women; 33-77 yr old) undergoing combined treatment for cancer of the stomach. Treatment included preoperative gamma irradiation from two opposite fields (400 rads/day, for 5 days, total dose 2,000 rads) followed by surgery (proximal resection, subtotal resection, or total gastrectomy). The basal gastrin level in the patients with cancer of the stomach was significantly greater than that in healthy controls (89.3 and 68.7 picog/ml, respectively). Gastrin levels did not depend upon the tumor localization. Preoperative gamma therapy produced significant decrease of gastrin levels in the patients with tumors located in the corpus and antral region of the stomach; gamma therapy did not affect gastrin level in the patients with tumors located in the proximal region of the stomach. Morphological examination of the surgery specimens showed that preoperative gamma therapy produced marked decrease in the number of G cells. Preoperative irradiation did not affect the functional activity of extragastric G cells. (15 Refs) (In RUS)

57. ESTROGEN RECEPTOR PROTEIN IN ADENOMAS OF THE LARGE BOWEL.

Agrez MV, Spencer RJ
(c/o Spencer) Dept. Colorectal Surgery, Mayo Clinic, 200 First St. Southwest, Rochester, MN, 55905
Dis Colon Rectum; 25(4):348-350 1982

Thirty adenomas of the large bowel, removed from 15 females and 15 males, were examined for the presence of estrogen receptor protein. The finding of positive binding capacity in 2 of the 30 adenomas supports the hypothesis that hormonal dependency does not play a major role in the development and growth of colorectal adenomas. (Author abstract) (15 Refs)

58. MALIGNANCY - METABOLIC MANIFESTATIONS OF CANCER.

Coombes RC
Ludwig Inst. for Cancer Res., London, England
J Appl Med; 8(5):361,363-365,367-368 1982

Cancer associated hormone-mediated syndromes are reviewed with reference to their possible role as tumor markers. Cushing's syndrome may be associated with small cell lung cancer and the syndrome of inappropriate antidiuretic hormone secretion is often associated with small cell carcinoma of the bronchus or a carcinoid tumor. Hypocalcemia, gynecomastic, hypertrophic osteoarthropathy, acromegaly, cachexia, hypoglycemia, gastrointestinal syndrome and neurological complications are all cancer-associated pathologies. (33 Refs)

59. HORMONE RECEPTORS IN COLON CANCER.

Zannini G, Contieri E
II Facolta di Medicina e Chirurgia, Universita di Napoli, Naples, Italy
Minerva Med; 73(18):1221-1224 1982

The hypothesis on the presence of specific hormone receptors in neoplasms of the colon was tested in 12 patients with primary multiple malignant tumors and on the effectiveness of adjuvant hormone therapy of 20 patients with inoperable malignant tumors of the digestive tract. Three of the 12 patients with primary multiple tumors had synchronous tumors, and the 9 others had metachronous tumors. Two of the three patients with synchronous tumors had adenocarcinomas of the colon and rectum, respectively, the third had carcinomas. In the nine patients with diachronous tumors the first tumors were located in the breast, larynx, uterus, ovary, thyroid gland and stomach, and the second tumors in the breast, colon, rectum, and sigmoid colon. The group of 20 patients (10 men and 10 women) with inoperable tumors were randomized into two groups. One group was (Group I) subjected to cyclic polychemotherapy, the other (Group II) to cyclic polychemotherapy with medroxyprogesterone acetate (MPA: 1,000 mg/day po). The evaluation after 12 mo showed an improvement concerning anorexia in 20% of the patients in Group I and in 70% in II, concerning dysphagia in 20% and 40%, concerning emesis in 10% and 40%, concerning asthenia in 20% and 70%, concerning pain in 20% and 60%, and concerning ability to work in 20% and 60%, respectively. The 1-yr survival rate were 30% in Group I and 70% in Group II. The findings indicate the effectiveness of adjuvant MPA therapy. (10 Refs) (In ITA)

60. ENDOCRINOPATHY ASSOCIATED WITH PINEAL TUMORS (1).

Mori K
Dept. Neurosurgery, Nagasaki Univ., Nagasaki 852, Japan
Neurol Med Chir (Tokyo); 21(4):359-363 1981

Origins, types, and hormonal production of pineal tumors are reviewed. Pineal gland tumors are broadly divided into germ cell tumors and pinealomas. Tumors with specific cell types are associated with human chorionic gonadotropin (HCG) or alpha fetoprotein production. Research on relationships between HCG-producing tumors and pubertas praecox is also discussed. (102 Refs) (In JPN)

61. THE DIFFUSE ENDOCRINE SYSTEM AND DERIVED TUMOURS. HISTOLOGICAL AND HISTOCHEMICAL CHARACTERISTICS.

van Bogaert LJ
Avenue Capitaine Piret 66 B, 1150 Brussels, Belgium
Acta Histochem (Jena); 70(1):122-129 1982

The Diffuse Endocrine System, to which the so-called APUD (Amine Precursor Uptake and Decarboxylation) cells do belong, gives rise to a group of tumors which may or may not secrete amines and/or polypeptide hormones: carcinoids (argentaffinomas, argentaffin or Kultschitzky cell carcinomas). Foregut carcinoids are predominantly of B type (trabecular), argyrophilic, or nonreactive (in about 70% of cases) to silver impregnation. Midgut tumors are generally of A type (insular); more than 80% of them are argentaffinic. Hindgut derived carcinoids are primarily of mixed type; nearly 70% are non-reactive to silver strains. From a cytological standpoint all types may be built up of either small-round, spindle-shaped, polyhedral or cuboidal cells. From a functional point-of-view, the cells are either clear and immature, non-reducing, reducing or exhausted. Accordingly, the diagnosis cannot be based alone on silver impregnation or other histochemical methods. (Author abstract) (43 Refs)

EFFECTS ON NORMAL AND NEOPLASTIC CELLS AND TISSUES

62. EFFECT OF ALTERED THYROID STATUS ON LYSOSOMAL ENZYMES AND THYMIDYLATE SYNTHETASE ACTIVITY IN TUMORS AND LIVERS OF HOST ANIMALS.

Al-Jurf AS, Suleiman SA, Erenberg AP
Dept. Surgery, Univ. Iowa, Iowa City, IA, 52242
J Surg Oncol; 20(1):21-24 1982

The purpose of this study was to determine whether or not alterations in tumor growth induced by changes in thyroid status were mediated through changes in key enzymes, whose activity is known to be influenced by thyroid hormones. The activities of three lysosomal enzymes (cathepsin B1, cathepsin D, and acid phosphatase) and thymidylate synthetase were measured in implanted mammary tumors as well as in the livers of host animals that were either euthyroid, hypothyroid, or hyperthyroid. Hypothyroidism produced no significant change in enzyme activity in the tumors. hyperthyroidism, on the other hand, did cause a significant increase in the activity of all lysosomal enzymes in the tumors, but did not affect thymidylate synthetase levels. In the livers of the host animals, hypothyroidism produced a significant decrease in cathepsin B1 and a significant increase in acid phosphatase but did not change cathepsin D or thymidylate synthetase levels. Hyperthyroidism produced a significant increase in all enzymes measured in the livers of the host animals. The significant decrease in tumor wt with hypothyroidism did not correlate with the insignificant changes in the enzymes tested. Similarly, there was no correlation between the significant increase in the enzymes levels found with hyperthyroidism and the insignificant change in tumor wt. (Author abstract) (28 Refs)

63. LONG-TERM EFFECT OF RADIATION ON THYROID FUNCTION AND TUMOR FORMATION.

Prinz RA, Oslapas R, Hofmann C, Shah KH, Ernst K, Refsguard J, Lawrence AM, Paloyan E
Res. Service, Hines Veterans Admin. Hosp., Hines, IL, 60141
J Surg Res; 32(4):329-337 1982

Cellular injury coupled with hypersecretion of thyroid stimulating hormone (TSH) is considered the mechanism for radiation-induced thyroid tumors. This hypothesis was tested by administering 40 uCi of 131I to male and female rats. Serum thyroxine (T4) decreased significantly overtime in male and female control and radiated animals. T4 was essentially the same in 6-and 12-mo-old radiated and control animals, but a significant decrease in T4 was noted in radiated females at 21 mo. TSH decreased overtime in control animals, but a significant increase in TSH was required in radiated animals to maintain T4 levels. Thyrocalcitonin (TC) was significantly greater in 21-mo-old control females than in males or radiated females. A significant increase in follicular cell thyroid neoplasms in radiated animals was associated with the elevated TSH levels. The importance of sex in thyroid tumor formation is illustrated by the fact that males had a significantly higher frequency of thyroid neoplasms than did females. C-cell hyperplasia and medullary thyroid carcinoma only occurred in control animals and accounted for their higher TC levels. This study confirms that administration of low doses of 131I leads to an increased frequency of thyroid tumor formation in rats and that direct cellular injury plus hypersecretion of TSH seem responsible for these radiation-induced tumors. (Author abstract) (18 Refs)

64. THE MODULATING OF ONOCOGENIC TRANSFORMATION INDUCED BY AGENTS AND MODALITIES USED IN CANCER THERAPY (MEETING ABSTRACT)

Borek C
College of Physicians and Surgeons, Columbia University, New York, NY
Conference on Cell Proliferation, Cancer and Cancer Therapy, February 17-19, 1982, New York, New York New York Academy of Sciences; :A18 1982

Agents which effectively control cancer in the human may also possess a significant oncogenic potential. Cell culture systems of both rodent and human origin serve as powerful tools to study the neoplastic potentials of these agents and to evaluate factor which modulate their transforming action. Our work indicates that the initiation of neoplastic transformation in vitro by x-rays is inhibited by maintaining the cells under hypothyroid condition; that the presence of triiodothyronine at doses as low as 10-12M at the time of radiation is essential for the induction of transformation. Similar results are being seen when the transforming agents is Cis platinum. Radiation induced oncogenesis is also inhibited by a variety of vitamin A analogs. This effect is excercised at the expression phase of transformation and is associated with membrane rather than chromosome changes. Additional work indicates that the oncogenic potential of x-rays and bleomycin is inhibited by superoxide dismutase; a free radical scavenger, a fact of potential interest in cancer therapy. (no Refs)

65. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.

Furth J
Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Hormones as etiological agents in neoplasia are discussed. The basic properties of human hormones are reviewed, and general considerations in the detection of hormonal activity are listed. Brief general comments are presented on tumors in peripheral areas illustrating the diversity of pathogenic mechanisms by which hormones can produce tumors. Peripheral tumors are of two kinds: those affecting non-hormone-secreting organs, which do not feed back (as with the mammary gland), and those affecting peripheral hormone-secreting organs, which do. The best example of the former is the mammary tumor, and good examples of the second type are thyroid and ovarian tumors. Other tumors which are hormonally related include adrenal tumors which are unique in that they can give rise to four or more types of tumors - estrogen, androgen, glucocorticoid, and mineralocorticoid secreting - and in that they have different types of inductive mechanisms. Renal cortical carcinomas are induced by estrogens in male hamsters. Human placental lactogen stimulates carcinogenesis in young rats. It promotes mammary tumorigenesis during pregnancy, both directly and indirectly, through its promotion of progesterone secretion by the ovary. Thyrocalcitonin is the hypocalcemic polypeptide hormone secreted by the medullary cells of the thyroid. These cells can give rise to medullary thyroid carcinoma. (286 Refs)

66. IMPAIRED REPAIR CAPACITY OF DNA STRAND BREAKS INDUCED BY 125I-TRIIODOTHYRONINE IN CHINESE HAMSTER CELLS.

Sundell-Bergman S, Johanson KJ
Gustav Werner Inst., Bos 532 S-751 22, Uppsala, Sweden
Biochem Biophys Res Commun; 106(2):546-552 1982

The induction of DNA strand breaks in Chinese hamster cells following (125I)-triiodothyronine (T3) labelling was investigated using the sensitive DNA unwinding technique. While nonradioactive T3 did not produce strand breaks, the 125iodinated form did. Effects of T3 were similar in V79, HeLa and GH1 cells. The inefficiency of DNA repair observed even after low 125I doses (0.4 dpm per cell) suggested that double strand breaks or more serious DNA damage had occurred. Results indicated that the 125I-decay products were within 60 nanometer from DNA, a distance at which 125I decay yields a high LET-type radiation. A comparison with previous work indicated that damage to DNA was more severe after (125I)-T3 than after incorporation of 125I directly into DNA. Possible reasons from this are discussed. These results suggest that the thyroid may not necessarily be the target organ for iodine isotope-induced radiation damage. Since a very high number of T3 receptors occur in the anterior pituitary, especially during growth, use of isotopes of this compound in children could result in disturbed hormone function. Another implication is the possible use of (125I)-T3 in therapy of tumors with a high number of nuclear receptors for T3. (17 Refs)

67. POTENTIATION OF THE THYMOSIN IMMUNOREGULATORY EFFECT BY HYPOCORTICOIDISM IN RATS WITH DMBA-INDUCED CARCINOGENESIS IN MAMMARY GLANDS.

Grinevich YA, Kamenets LY
Kiev Roentgen-Radiological and Oncological Res. Inst., Health Ministry of Ukrainian SSR, 252022 Kiev, USSR
Neoplasma; 29(1):19-27 1982

Effect of adrenalectomy and or thymosin administration on the tumor growth and immunity system were investigated on the models of 7,12-dimethylbenz(a)anthracene(DMBA)-induced mammary neoplasms in rats. Adrenalectomy and thymosin administration resulted in antitumorigenic action, whereas maximal inhibiting effect was achieved after thymosin injection in adrenalectomized animals. The maximal antitumorigenic effect of thymosin in adrenalectomized rats was accompanied by synergistic immunopotentiating effect of thymosin and adrenalectomy. Immunorehabilitation with thymosin and simultaneous correction of hormone production in the adrenal cortex are believed to enhance the effectiveness of therapy in cancer patients (Author abstract) (29 Refs)

68. DIRECTED EFFECTOR CELLS SELECTIVELY LYSE HUMAN TUMOUR CELLS.

Simone CB
Clinical Pharmacology Branch, Div. Cancer Treatment, NCI, Bethesda, MD, 20205
Nature; 297(5863):234-236 1982

Effects of classical antibody-dependent cellular cytotoxicity (ADCC) were compared with those of 'directed' ADCC using trinitrophenyl (TNP)-modified targets. Peripheral blood lymphocytes or neutrophils were added to anti-TNP labeled targets (classical ADCC), or effector cells with attached anti-TNP antibody ('directed' ADCC) were added to TNP-labelled targets. The three targets used were TNP-resealed human RBC ghosts containing carboxyfluorescein (CF), TNP-51CR-labeled intact human RBC, and TNP-51CR-labeled MCF-7 breast cancer cells. Effector cells alone or effector cells treated with polyethylene glycol and phthalate oils, used to attach antibody to effectors cells, produced minimal background release from each target. Directed effector cells mediated marker release from a membrane model (RBC ghosts), from intact RBC, and from MCF-7 cells. Thus attachment of antibody to effector cells did not inhibit cell-mediated killing. The specificity of the directed cytotoxic effector cells was assayed by placing two antigenically distinct targets in the same microtiter well: TNP-modified ghosts containing CF and human choriocarcinoma cell line JEG-3. JEG-3 cells were chosen as targets because the anti-human chorionic gonadotropin (anti-HCG)-directed effector cell-JEG-3 system may be a model clinically relevant to human testicular cancer. One thousand nanog/ml or more of human chorionic gonadotropin (HCG) almost totally prevented anti-HCG-directed effectors from lysing 51CR-labeled JEG-3 cells. Anti-human Leu 1 reagent was used to see whether it would effect lysis of targets in vitro after it had been attached to effector cells. (20 Refs)

69. EFFECTS OF MEDROXPROGESTERONE ACETATE ON THE DEVELOPMENT OF DIMETHYLBENZANTHRACENE-INDUCED MAMMARY TUMORS. POSSIBLE MODES OF ACTION (MEETING ABSTRACT)

Danguy A, Legros N, Leclerq G, Heuson JC
Laboratory of Histology and Laboratory of Mammary Oncology, Brussels, Belgium
International Symposium on Medroxyprogesterone Acetate, February 24-26, 1982, Geneva, Switzerland. Farmatalia Carlo Erba 91 pp., 1982.

Our purpose was to describe the effects of different doses of Medroxyprogesterone acetate (MPA) on growth of 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors and to study the underlying endocrine mechanisms. This experimental model is extensively studied in order to understand the hormonal dependency of human breast cancer. MPA was administered sc at doses of 1 mg/kg, 10 mg/kg and 100 mg/kg 6 days a week for 6 weeks. The smaller dose enhanced tumor growth whereas the higher one was significantly inhibitory. The administration of 100 mg/kg/day of the drug to ovariectomized rats significantly inhibited the increase in body weight as compared to ovariectomy alone. In the animals treated with 10 and 100 mg/kg/day the ovaries contained very small follicles and no corpora lutea; the adrenals were also distinctly small with atrophy of the cortical components. Using sensitive histological (Peroxidase anti-Peroxidase Complex unlabelled antibody stain, immunofluorescence) and endocrine (Radioimmunoassay) techniques we were able to demonstrate the modifications produced by MPA in the pituitary gland and the serum: atrophy of adenocorticotropes, gonadotropes and mammotropes as well as decrease in plasma Luteinizing Hormone (LH) and Prolactin (PRL). So the antitumor activity of MPA may be explained by a partial pharmacological hypophysectomy. However it remains possible that part of the inhibitory action of MPA may be exerted directly at the tumor level. Indeed, the action of MPA via the progesterone receptor and a direct cytotoxic effect of the drug must be drawn into consideration. (no Refs)

70. EFFECTS OF ANTIBODIES TO CHORIOGONADOTROPIN IN MALIGNANT GROWTH. I. RAT 3230 AC MAMMARY ADENOCARCINOMA.

Kellen JA, Kolin A, Acevedo HF
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Cancer; 49(11):2300-2304 1982

To determine whether the in vivo production of antibodies against choriogonadotropin (CG) could modify the relationship between host and malignant growth, the effects of preimmunization with a conjugate of the beta-subunit of CG and tetanus toxoid (CGbeta-tt) on the development and growth of lung metastasis following iv injection of R 3230 rat mammary adenocarcinoma cells into Fischer 344 female rats have been investigated. This neoplasm has been previously demonstrated to synthesize CG-like material. A test group of 70 animals and two matched control groups of 15 animals each were used. One of the control groups was untreated and the other received tetanus toxoid only. All the control animals had multiple lung foci of neoplastic cells 10 days after seeding, as has been previously observed, and CG antibodies were undetectable. In contrast, a significant titer of anti-CG was found in all preimmunized animals. At the same time, the pretreated animals rarely had a few small neoplastic nodes in the entire lung sections at the standard 8-10 days post-seeding. The protective effects of preimmunization with CGbeta-tt were further demonstrated by the animals living 20 days post-seeding, the absence of lung pathology in the ones killed thereafter, and by six animals that were left alive and have not shown any deterioration for more than 6 mo after the administration of the cell suspension. (Author abstract) (38 Refs)

71. PLATELET FUNCTION ABNORMALITIES IN ACUTE LEUKAEMIA.

Ramos OF, Moron EC, De Castro Arenas R
Hospital Militar Central 'Dr. Carlos J. Finlay', Calle 114 y Ave. 31, Marianao, Ciudad de la Habana, Cuba
Haematologia (Budap); 14(4):383-391 1981

Platelet function abnormalities were studied in 14 patients (9 males, 5 females, 3-83 yr old) with various forms of acute leukemia. Four patients had acute lymphoblastic leukemia, five acute myeloblastic leukemia (AML) without maturation, two AML with maturation, and three myelomonocytic leukemia. All patients were studied prior to chemotherapy. Thrombocytopenia was associated with a considerably abnormal platelet function. All patients showed deficient clot retraction. Availability of platelet factor 3 was abnormal in 6 patients and bleeding time was prolonged in 4 but without statistical differences from 12 health controls. Aggregation was different with various agents tested. Thirteen patients demonstrated abnormal collagen-induced aggregation while 10 had impaired aggregation with epinephrine. Thus, with four exceptions, an abnormal aggregation was always associated with abnormal epinephrine-induced aggregation. Aggregation with adenosine diphosphate was impaired in seven patients and three showed a slightly but not significantly decreased ristocetin-induced aggregation. Two patients in complete remission showed improvement in their platelet function. A good correlation was observed between bleeding diathesis and abnormalities in bleeding time, clot retraction, and aggregation induced by collagen and epinephrine. Prothrombin time and activated partial thromboplastic time were normal in all patients. Results suggested that the defect in leukemic platelets is due to the leukemic process itself. (21 Refs)

72. TUMOR DEVELOPMENT IN THE HUMAN COLON IS ENHANCED BY EPIDERMAL GROWTH FACTOR (UROGASTRONE), DEOXYCHOLIC ACID, AND AN ENDOGENOUS ANALOG TO TPA (MEETING ABSTRACT)

Friedman EA
Memorial Sloan-Kettering Cancer Center, New York, NY
Conference on Cell Proliferation, Cancer and Cancer Therapy, February 17-19, 1982, New York, New York New York Academy of Sciences; :AP-5 1982

Many human neoplasms arise through a series of progressive cellular changes. Premalignant cells in the colon form a benign tumor or adenoma, from which a carcinoma develops. Benign tumors fall into three classes based on their pathology and clinical prognosis. Premalignant epithelial cells cultured from each class reflect the tumor's position in the progression to carcinoma. Cells from early-stage (tubular) adenomas are stimulated to divide by EGF(epidermal growth factor) (structurally similar to urogastrone, a tropic hormone in the intestine), by TPA (12-O-tetradecanoylphorbol-13-acetate), and by deoxycholic acid, a secondary bile acid found in the colon. Cells from either intermediate-stage (villotubular) or late-stage (villous) adenomas are not stimulated to divide by EGF or by deoxycholic acid. TPA-treated intermediate and late-stage premalignant cells from rills and clusters several cells in thickness and secrete a plasminogen activator. This multilayering is reminiscent of areas of carcinoma found within adenomas. Furthermore, it suggests that a endogenous compound which binds to TPA receptors on late-stage premalignant cells, and so mimics TPA activity, is important in the transition to malignancy. (no Refs)

73. A POSSIBLE ROLE OF HORMONES ON HEPATOCYTE AND HEPATOMA CELL PROLIFERATION (MEETING ABSTRACT)

Coetzee ML, Ove P
Department of Anatomy and Cell Biology, University of Pittsburgh, Pittsburgh, PA
Anat Rec; 202(3):33A 1982

Evidence is provided that proliferation of hepatocytes and transplantable Morris hepatoma 7777 might to some extent be regulated by triiodothyronine (T3), the adrenals and/or a specific serum protein, the levels of which are correlated with serum T3 levels. We have reported elevated levels of the serum protein following partial hepatectomy and a single injection of T3 and both are correlated with increased hepatic DNA synthesis. Both the cell proliferation of hepatoma 7777 and the circulating levels of the serum protein were decreased in thyroidectomized rats. When serum protein levels were elevated as a result of removal of 70% of the liver or a single injection T3, prior to transplant, accelerated hepatoma growth was observed. A tumor implanted into the back rather than in the thigh can be easily excised after 10 days with little injury to the animal. When this original transplant was surgically removed, serum protein levels rise rapidly and remain elevated for some time. A 2nd hepatoma transplant now grows at an accelerated rate. Both serum T3 and thyroxine (T4) levels are extremely low following thyroidectomy, but T3 levels are dramatically increased in hepatoma-bearing animals, while T4 levels remain constant. Adrenalectomy, performed 24 or 48 hr prior to partial hepatectomy, enhanced the response of increased DNA synthesis. On the other hand, dexamethasone, injected 48 hr prior to partial hepatectomy, completely inhibited the dramatic burst of hepatic DNA synthesis that usually occurs 20 hr post-operatively. (1 Ref)

74. DIRECT CYTOCHEMICAL LOCALIZATION OF CATALYTIC SUBUNITS DISSOCIATED FROM CAMP-DEPENDENT PROTEIN KINASE IN REUBER H-35 HEPATOMA CELLS. II. TEMPORAL AND SPATIAL KINETICS.

Byus CV, Fletcher WH
Div. Biomedical Sciences, Dept. Biochemistry, Univ. California, Riverside, CA, 92521
J Cell Biol; 93(3):727-734 1982

The activation of cyclic AMP-dependent protein kinase results in the release of the catalytic subunit which, similar to the free enzyme, possesses phosphotransferase activity for a variety of specific protein substrates. Using a cytofluorometric technique we monitored the appearance of free catalytic subunit in Reuber H35 hepatoma cells in culture after incubation with N(6)-1'-O-dibutyryl-cyclic AMP (DBcAMP), 8-bromoadenosine-3':5'-cyclic monophosphate (8-BrcAMP), and glucagon. The cytochemical method employs the heat-stable inhibitor of the free catalytic subunit which has been conjugated to fluorescein isothiocyanate (F:PKI). Here we studied the temporal and spatial kinetics of the free catalytic subunit following activation of cAMP-dependent protein kinase by increasing concentrations of DBcAMP,8-BrcAMP, and glucagon. Under similar conditions protein kinase activation was also assessed biochemically in H35 cell supernatants by assaying the protein kinase activity ratio. Incubation of the hepatoma cells with DBcAMP led to an increase in the activity ratio. During the same period using the F:PKI probe, a significant increase in cytoplasmic and nucleolar fluorescence indicative of the release of the free catalytic subunit was coincidentally observed. Discernible nucleoplasmic fluorescence did not occur until 1 hr after the addition of DBcAMP. Cultures incubated with 8-BrcAMP exhibited a more rapid activation of the protein kinase measured cytochemically. Cultures incubated with 8-BrcAMP had significantly increased cytoplasmic and nucleolar fluorescence compared to unstimulated cells. The results reported herein suggest that both cyclic nucleotide analogues and a polypeptide hormone lead to the activation of cAMP-dependent protein kinase in similar intracellular compartments in Reuber H35 hepatoma cells. The appearance of protein kinase catalytic subunit in the nucleolus also serves to support earlier reports which suggest a biological role for this enzyme in the nucleus. (33 Refs)

75. THE EFFECT OF INSULIN ON COLLAGEN PRODUCTION IN ISOLATED CHONDROSARCOMA CHONDROCYTES.

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Dept. Biochemistry, Medical Coll. Virginia, Richmond, VA, 23298
Biochem Biophys Res Commun; 106(2):338-345 1982

Evidence is presented that several anabolic processes of isolated chondrosarcoma chondrocytes are stimulated by physiological concentrations of insulin. The rates of incorporation of both (3H)-proline and (35S)-sulfate into macromolecules during 2 hr exposure periods for control chondrocytes remained relatively constant. In contrast, uptake of (3H)-uridine by control cells was initially rapid (1-3 hr), declined (3-5 hr) and remained relatively constant thereafter (5-7 hr), suggesting the presence of a rate limiting factor(s). Insulin induction increased the amount of label incorporated into macromolecules from proline and sulfate by stimulating net synthesis. The increase in sulfation apparently reflected an increase in proteoglycan synthesis because sulfate freely diffuses into cells and is not compartmentalized. Insulin induction increase the amount of label incorporated into RNA from (3H)-uridine, due partially to insulin's ability to prevent the rapid decline of the rate of uptake seen in control cells. This may reflect an increase in the specific activity of the uridine triphosphate pool. Chondrosarcoma chondrocytes responded to a range of insulin concentrations that were physiological meaningful, making this system well suited for metabolic and hormonal mechanism of action studies. (14 Refs)

76. SOMATOSTATIN-REDUCED PROLIFERATION OF MURINE APLASTIC CARCINOMA CONDITIONED TO DIABETES.

Vuk-Pavlovic S, Bozikov V, Pavelic K
Inst. Immunology, Rockefellerova 2, 41000 Zagreb, Croatia
Int J Cancer; 29(6):683-686 1982

Murine mammary aplastic carcinoma, when it is passed from one alloxan-diabetic animal to another, after several passages becomes conditioned to hypoinsulinemia by secreting its own substance(s) immunologically cross-reactive with insulin (SICRI). Although not cytotoxic, the total daily dose of 2.5 mg of synthetic linear somatostatin per 1 kg body mass, administered in three or more portions, retards tumor growth in normoinsulinemic mice and the proliferation of tumors preconditioned by three serial passages in diabetics. After the first passage, somatostatin treatment has no effect on the already slow growth of the unconditioned tumor. Somatostatin-reduced tumor proliferation is accompanied by the strong suppression of insulin and SICRI levels, respectively; this effect is completely abolished by the administration of modest doses of crystalline insulin. It is concluded that somatostatin retards tumor growth by diminution of plasma levels of insulin and SICRI, respectively. (Author abstract) (13 Refs)

77. DIMETHYLHYDRAZINE-INDUCED COLONIC NEOPLASIA: DISSOCIATION FROM ENDOGENOUS GASTRIN LEVELS.

Oscarson JE, Veen HF, Ross JS, Malt RA
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Surgery; 91(5):525-530 1982

The potential tropic effect of gastrin in promoting colonic carcinogenesis was tested in rats (n = 133) with 6-to 16-fold variations in endogenous gastrin resulting from antrectomy or fundectomy, followed by 12 injections of 1,2-dimethylhydrazine (10 mg/kg). The incidence and grade of differentiation of resulting tumors, as well as the thickness, content of nucleic acids, and specific activity of DNA in colonic mucosa, were similar in both high-gastrin and low-gastrin animals and were unchanged from data in unoperated control animals receiving only the carcinogen. Long-term changes in endogenous gastrin concentration are not followed by colonic mucosal tropic effects, and gastrin does not act as a cofactor in dimethylhydrazine-induced carcinogenesis at this dosage. (Author abstract) (25 Refs)

78. VASOPRESSIN: ACTION OF WRK-1 RAT MAMMARY TUMOR CELLS.

Monaco ME, Kohn PH, Kidwell WR, Strobl JS, Lippman ME
Veterans Admin. Hosp., 16 West, 408 First Ave., New York, NY, 10010
JNCI; 68(2):267-270 1982

WRK-1, a cell line in long-term culture derived from a 7,12-dimethylbenz[a]anthracene-induced rat mammary tumor, responds to physiologic concentrations of vasopressin with increased precursor incorporation into phospholipids and with increased protein accumulation. Because vasopressin has been reported to be a potent mitogen for HeLa cells and 3T3 cells, a study was conducted to determine whether it could act as a mitogen for WRK-1 cells. Under no conditions was a clear-cut mitogen response to vasopressin demonstrated. (Author abstract) (14 Refs)

79. CHOLECYSTOKININ INHIBITS NITROSAMINE-INDUCED CARCINOGENESIS (MEETING ABSTRACT)

Johnson FE, LaRegina MC, Martin SA, Bashiti HM
St. Louis University Medical Center, St. Louis, MO
Joint Meeting of the Society of Surgical Oncology and Society of Head and Neck Surgeons, April 18-23, 1982, Marco Island, Florida. The Society of Surgical Oncology and the Society of Head and Neck Surgeons 265 pp., 1982.

Acute administration of cholecystokinin (CCK) has well-known effects on gall bladder contractions and pancreatic-biliary secretion. Recent data indicates that chronic administration of CCK has trophic effects on abdominal viscera, particularly pancreas. In order to determine whether CCK enhances malignant growth as well as growth of normal organs, we administered CCK together with di-isopropanol nitrosamine (DIPN), a carcinogen known to induce pancreatic, hepatic (and other) carcinomas. Two hundred young male Syrian golden hamsters (approx 60 gm) were divided into four groups. Group A (80 animals received DIPN (250 mg/kg) plus CCK (20 U/kg) by weekly subcutaneous injections; Group B (80 animals), DIPN alone; Group C (20 animals), CCK alone; Group D (20 animals), saline. Injections were done for 40 weeks, with animal sacrifice and autopsy at 10, 14, 18, 27, and 40 weeks. Microscopic study of pancreas, liver, heart, lung, brain, spleen small intestine, large intestine, testis, kidney, and stomach was carried out in each animal. Animal weights and visceral weights showed no striking differences between groups. Microscopic examination of the pancreas showed: DIPN induced pancreatic and hepatic carcinomas; CCK administration appeared to prevent their development. The mechanism of this effect is unknown. These results have implications for human carcinogenesis, and some of the implications are testable by currently available methods. (no Refs)

80. DECREASED STEROID PRODUCTION IN ACTH-PRETREATED Y-1 ADRENAL TUMOR CELLS RELATED TO CAMP-DEPENDENT PROTEIN KINASE ACTIVATION (MEETING ABSTRACT)

Murray SA, Byus CV, Fletcher WH
Department of Biochemistry, University of California, Riverside, CA
Anat Rec; 202(3):134A 1982

Y-1 mouse adrenal cortical tumor cells increase the production of steroids and cAMP while decreasing DNA synthesis in response to ACTH. ACTH pretreated cells become resistant to the effect of subsequent ACTH on steroid production, cAMP synthesis, and the inhibitory effect on DNA synthesis. DB cAMP pretreatment of the Y-1 cells results in a resistance of cells to respond to ACTH or further dB or 8BrcAMP in terms of steroid production. Employing a fluorescinated conjugate of the heat stable inhibitor protein as a specific and sensitive cytochemical probe we have examined the temporal and spatial kinetics of catalytic subunit (C) dissociated from the cAMP-dependent protein kinase holoenzyme at a single cell level of resolution. When Y-1 adrenal cells were stimulated with ACTH (0.5-50 milliunits/ml) for 30 second to 1 hour cAMP-dependent protein kinase was dissociated in a dose and time dependent manner. Free C appeared first in the cytoplasm and in the nucleolus and with time nuclear fluorescence was observed. Y-1 adrenal cells pretreated with ACTH or DB cAMP had a decreased activation of the kinase following subsequent ACTH treatment. (no Refs)

81. ELECTRON MICROSCOPIC AND CYTOCHEMICAL OBSERVATIONS OF THEOPHYLLINE AND MELANOCYTE-STIMULATING HORMONE EFFECTS ON MELANOMA CELLS IN CULTURE.

Hu F, Mah K, Teramura DJ
Oregon Regional Primate Res. Center, Beaverton, OR, 97006
Cancer Res; 42(7):2786-2791 1982

The effects of theophylline and melanocyte-stimulating hormone on B16 melanoma cells in culture were studied by electron microscopy and dopa cytochemistry. The data show that theophylline and melanocyte-stimulating hormone enhance melanogenesis by activating tyrosinase synthesis and its transfer but that neither affects the synthesis of the well-organized eumelanosome matrix. Their pigmenting effects appear to be limited to the melanogenic cells and result from a marked increase, particularly in theophylline-treated cells, in pheomelanosome formation. (Author abstract) (16 Refs)

82. GROWTH FACTORS FOR CULTURED MAMMARY AND FIBROBLASTIC CELLS (MEETING ABSTRACT)

Rudland PS, Smith JA
Ludwig Institute, Royal Marsden Hospital, Sutton, Surrey, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

The growth of the mammary gland is controlled by a series of interacting mammotrophic hormones. However these hormones are relatively inactive compared with serum or novel, semi-purified growth factors (GF) in stimulating cell proliferation of cultured rat mammary gland epithelial cells. These GF's are of two types, a pituitary GF exerting systemic control and GF's from surrounding cells which may exert local control of mammary epithelial cell proliferation. The effects of the GF's can be amplified by certain mammotrophic hormones (eg insulin: I and hydrocortisone: HC). As in the mammary gland, GF's such as FGF, EGF, PGF2 alpha (fibroblast growth factor, epidermal growth factor, prostaglandin F2alpha) can stimulate DNA synthesis in quiescent 3T3 fibroblasts and this can be modified with I and HC. To explain the kinetics obtained with PGF2 alpha and FGF two operational signals are postulated, signal (1) initiates a lag phase and signal (2) determines the magnitude of the rate of cellular entry into the S phase of the cell cycle. Usually the rate of entry into S governs the rate of cell division, but when serum is completely removed additional components (eg transferrin) are required. During the lag phase the pathways generated by signal (1) and signal (2) have to interact causing increases in hypothetical protein(s) inside the cell. One of the altered properties of virally transformed cells is their lack of response to GF's. In the two cases examined by other groups the viral transforming proteins directly act on the putative intracellular pathways leading to increased cell proliferation rates. (no Refs)

EFFECTS OF ENDOGENOUS AND EXOGENOUS AGENTS ON NON-STEROID HORMONE ACTIVITY

83. PITUITARY RESPONSES TO THYROTROPIN-RELEASING HORMONE AFTER TREATMENT WITH THE BREAST CARCINOGEN NITROSOMETHYLUREA: INHIBITION OF PROLACTIN BUT NOT THYROTROPIN RELEASE.

Kieffer JD, Maloof F, Vickery AL, Mover H, Downing M, Ridgway EC
Thyroid Unit, Massachusetts General Hosp., Boston, MA, 02114
Endocrinology; 110(6):1892-1896 1982

N-Nitrosomethylurea (NMU) is a widely used experimental breast carcinogen. The present report describes the effects of NMU on the plasma PRL and TSH increases in response to exogenous TRH. Female Buffalo rats, 75-80 days old, were given a single ip injection of NMU (10 mg/100 g) or vehicle. At various times after injection, NMU-treated rats and vehicle-injected controls were tested with exogenous TRH (625 ng/100 g, ip). Groups of four to six rats were bled at 10, 20, 30, 45, and 60 min after TRH and at 10 min after saline (baseline group). The response to TRH (delta) was determined by subtracting the mean plasma PRL or TSH level of the baseline group from the mean peak level observed after TRH. For four separate control experiments, deltaPRL averaged 104 +-19 ng/ml (mean +- SE). At 20 hr, 42 hr, 6 days, and 2, 3, 4, 8, and 12 wk after NMU, deltaPRL was 87, 0, 0, 16, 10, 3, 49, and 65 ng/ml, respectively. deltaPRL was statistically significant in all four control experiments, and remained significant at 20 hr after NMU. However, from 42 hr through 4 wk, no significant deltaPRL occurred. A significant deltaPRL reappeared at 8 and 12 wk, the approximate time of appearance of the first palpable breast cancers. Pituitary PRL concentrations (micrograms PRL per mg protein) were significantly lower in NMU-treated groups than in vehicle-treated controls at 42 hr, 3 wk, and 12 wk. In contrast to its marked inhibitory effect on deltaPRL, NMU had no effect on deltaTSH. This is consistent with the hypothesis that treatment with NMU resulted in a selective impairment of pituitary PRL-secreting cells. Moreover, our data show that the plasma PRL response to TRH was inhibited at times after NMU when pituitary PRL was not significantly depleted. This observation is in accord with the concept of impairment of either TRH receptor binding or events which couple receptor binding and hormone release. (Author abstract) (38 Refs)

84. ENHANCEMENT OF DMBA INDUCED MAMMARY TUMOURS BY INTERMITTENT WHOLE BODY HYPERTHERMIA (42 C).

Lahiri T, Deomina N, Dedov II, Lahiri P
Chittaranjan Natl. Cancer Res. Centre, Calcutta, India
Endocrinol Jpn; 28(5):569-574 1981

Effects of intermittent whole body hyperthermia (42 C) on dimethyl benz-anthracene (DMBA)-induced rat mammary tumors were determined in terms of tumor growth, plasma hormone levels, and activity of pituitary prolactin cells.

Female Wistar (50-55 days old) rats were used. Heat exposure resulted in significant growth stimulation of the tumors in the majority (16/20) of heat-treated rats, compared to rats maintained at 25 C. The growth of tumors was generally intensified after 2-3 wk of heat stress and at the end of 6 wk an approx seven-fold increase in tumor vol was observed. Histological examination revealed that 18/20 animals in the control group and 17/20 in the treated group had adenocarcinoma type tumors. Other tumors were fibroadenomas and they were not included into the study. Body wt and wt of adrenal glands in heat-exposed rats were increased, while the wt of uterus and thymus was decreased. Plasma estradiol level in heat stressed animals was lowered while values for total thyroxine and thyroid stimulating hormone showed no fluctuation. Serum prolactin level was significantly increased in the heat exposed group. An electron microscopy study of prolactin cell activity of pituitary revealed that in heat stressed animals the activity was greater than in rats maintained at room temperature. Results indicated that whole body hyperthermia definitely enhances DMBA-induced mammary tumors in rats and the differences in response pattern might be related to the mode of heat application, etiology, or hormonal sensitivity of tumors. (20 Refs)

85. INSULIN RELEASE AND PROTEIN PHOSPHORYLATION: POSSIBLE ROLE OF CALMODULIN.

Schubart UK, Erlichman J, Fleischer N
Dept. Medicine and Diabetes Res. and Training Center, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Fed Proc; 41(7):2278-2282 1982

Both Ca++ and cyclic AMP (cAMP) are implicated in the regulation of insulin release in the pancreatic beta cell. In hamster insulinoma cells used in our laboratory to study the mechanism of insulin release, Ca++ and cAMP trigger secretion independently. Concomitant with stimulation of the secretory apparatus both cAMP and Ca++ promote phosphorylation of distinct insulinoma cell proteins. Calmodulin may be involved in the stimulation of insulin release and protein phosphorylation induced by Ca++ influx. The Ca++-dependent protein kinase of the insulinoma cell is activated by exogenous calmodulin and blocked by trifluoperazine, an inhibitor of calmodulin action. This drug also inhibits glucose-induced insulin release in pancreatic islets. In insulinoma cells trifluoperazine blocks Ca++ influx-mediated insulin release and protein phosphorylation with no effect on basal or cAMP-mediated secretion. Inhibition of Ca++ influx-mediated insulin release and protein phosphorylation occurs with nearly identical dose dependence. Inasmuch as trifluoperazine affects voltage-dependent Ca++ uptake in insulinoma cells, an involvement of calmodulin cannot be directly inferred. The evidence suggests that protein phosphorylation may be involved in the activation of the secretory apparatus by both cAMP and Ca++. It is proposed that stimulation of insulin release by cAMP and Ca++ is mediated by cAMP-dependent protein kinase and calmodulin-dependent protein kinase, respectively. (Author abstract) (43 Refs)

86. EFFECT OF TUNICAMYCIN ON INSULIN BINDING AND ON PROTEOGLYCAN SYNTHESIS AND DISTRIBUTION IN SWARM RAT CHONDROSARCOMA CELL CULTURES.

Stevens RL, Schwartz LB, Austen KF, Lohmander LS, Kimura JH
Dept. Medicine, Harvard Medical Sch., Boston, MA, 02115
J Biol Chem; 257(10):5745-5750 1982

Tunicamycin, an inhibitor of dolichol-diphospho-N-acetylglucosamine formation and hence an inhibitor of N-linked oligosaccharide biosynthesis, suppressed total proteoglycan synthesis by Swarm rat chondrosarcoma chondrocytes without affecting the size of the proteoglycan molecule, its secretion from the cell, or its ability to be retained in the extracellular matrix. In addition, tunicamycin did not substantially alter the ability of the chondrocytes to polymerize glycosaminoglycan onto an exogenous beta-D-xyloside acceptor. A secondary effect of tunicamycin suppression of proteoglycan synthesis was that a lesser amount of newly synthesized proteoglycan diffused from the extracellular matrix into the culture medium. The ability of exogenous hyaluronic acid and proteoglycan to increase the percentage of newly synthesized 35S-proteoglycan in the medium in tunicamycin-treated cultures indicates that matrix retention of 35S-proteoglycan is related to the total extracellular uronic acid content rather than to the presence or absence of mannose oligosaccharides bound to the proteoglycan molecule. These noncytotoxic concentrations of tunicamycin (33-333 ng/ml) decreased [3H]mannose incorporation to the same extent that they decreased total [35S]sulfate and [3H]serine incorporation, and caused the chondrocyte to synthesize and secrete a species of beta-hexosaminidase that was mannose-deficient as assessed by its failure to bind to concanavalin A. The additional finding of decreased insulin binding to tunicamycin-treated chondrosarcoma chondrocytes suggested that the inhibition of proteoglycan synthesis was due to diminution of receptors which respond to stimulatory hormones. (Author abstract) (24 Refs)

87. PANCREATIC ENDOCRINE FUNCTION IN LEUKEMIC CHILDREN TREATED WITH L-ASPARAGINASE.

Meschi F, Di Natale B, Rondanini GF, Uderzo C, Jankovic M, Masera G, Chiumello G
Clinica Pediatrica III, Ospedale L. Sacco, Via G.B. Grassi, 74, I-20157 Milan, Italy
Horm Res; 15(4):237-241 1981

The effect of arginine infusion on blood glucose and plasma levels of insulin, C-peptide and glucagon has been studied in leukemic children before and after treatment with L-asparaginase (10,000 U/m2/day for 10 days). Therapy induced a significant reduction in basal and peak blood glucose, insulin and C-peptide levels, while glucagon was unmodified. The conserved C-peptide-insulin molar ratio suggests the interference of L-asparaginase with proinsulin synthesis. In conclusion our results prove a decreased insulin reserve with a preserved, although reduced, beta-cell function. (Author abstract) (11 Refs)

88. EFFECT OF TAMOXIFEN ADMINISTRATION ON PROLACTIN RELEASE BY INVASIVE PROLACTIN-SECRETING PITUITARY ADENOMAS.

Lamberts SW, Verleun T, Oosterom R
Dept. Medicine III, Univ. Hosp. Dijkzigt, 40, Dr. Molewaterplein, 3015 GD Rotterdam, The Netherlands
Neuroendocrinology; 34(5):339-342 1982

Bromocriptine treatment of patients with invasive prolactin (PRL)-secreting pituitary adenomas does not invariably result in normalization of the plasma PRL levels. We previously showed that the antiestrogenic drug tamoxifen inhibited hormone release from transplantable PRL-secreting pituitary tumors in rats. In eight patients with invasive PRL-secreting pituitary adenomas with extrasellar extension, the effect of the administration of tamoxifen was investigated on the plasma PRL concentration and on the bromocriptine-mediated inhibition of PRL release. Treatment for 5 days with tamoxifen (20 mg/day) suppressed plasma PRL levels as measured in 5 samples over the day significantly by 20 +-3% (means +- SEM; p less than 0.01). During tamoxifen administration the inhibition of PRL secretion by 2.5 mg bromocriptine was further suppressed by 36 +-7%, in comparison with the plasma PRL levels after bromocriptine alone p less than 0.01). Tamoxifen administration suppressed PRL release in patients with giant invasive PRL-secreting pituitary adenomas, and it had a slight but significant additive or potentiating effect on the bromocriptine-mediated inhibition of PRL secretion. However, despite the simultaneous administration of bromocriptine and tamoxifen, normalization of the circulating PRL levels was not reached in this type of patient. (Author abstract) (12 Refs)

89. EFFECTS OF CRANIAL RADIATION ON HYPOTHALAMIC-ADENOHYPOPHYSEAL FUNCTION: ABNORMAL GROWTH HORMONE SECRETORY DYNAMICS.

Chrousos GP, Poplack D, Brown T, O'Neill D, Schwade J, Bercu BB
NIH, Building 10, Room 13N260, Bethesda, MD, 20205
J Clin Endocrinol Metab; 54(6):1135-1139 1982

The function of the hypothalamic-adenohypophyseal unit was tested in two groups of rhesus monkeys before and at periodic intervals after the administration of 2,400 and 4,000 rads cranial radiation. This therapy was given in 10 fractions over a 2-wk period. Plasma TSH, basally and after TRH administration, and LH and FSH, before and after gonadotropin-releasing hormone stimulation, were normal up to 1 yr after radiation. Plasma GH at the basal state and after arginine and L-dopa stimulation was also normal. An insulin tolerance test, however, demonstrated a blunted GH response at a dose (0.1 U/kg) that caused brisk stimulation of GH secretion in normal control monkeys. A larger dose of insulin (0.2 U/kg) resulted in ample secretion of GH in these animals, suggesting decreased hypothalamic sensitivity to insulin in treated animals. The measurement of GH every 20 min for 24 hr in animals treated with 4,000 rads showed a dramatically altered secretory pattern of GH 1 yr after radiation. GH secretory spikes were markedly decreased in both frequency and amplitude, suggesting a reduction in the normal daily production of GH. (Author abstract) (28 Refs)

90. MENSTRUAL FUNCTION AND SERUM PROLACTIN LEVELS AFTER LONG-TERM BROMOCRIPTINE TREATMENT OF HYPERPROLACTINAEMIC AMENORRHOEA.

Bergh T, Nillius SJ, Wide L
Dept. Obstetrics and Gynecology, Clinical Chemistry, Univ. Hosp., S-750 14 Uppsala 14, Sweden
Clin Endocrinol (Oxf); 16(6):587-593 1982

Long-term bromocriptine treatment was discontinued in 37 women with hyperprolactinemic amenorrhea. After cessation of therapy 30 of the 37 women became hyperprolactinemic again with amenorrhea or anovulatory bleeding. Seven of the women continued to have regular ovulatory menstruation but only three were normoprolactinemic 3 months after stopping treatment. Two of the seven women had evidence of pituitary tumor regression. After the discontinuation they had nearly normal prolactin levels but during 2 years of follow up the serum prolactin levels slowly increased. In the 27 women with pre-treatment prolactin levels below 100 ug/l there was no difference between the prolactin levels before starting and 1 month after stopping treatment, while the women with pre-treatment prolactin levels above 100 ug/l had lower levels after therapy. Bromocriptine treatment seldom results in permanent cure of hyperprolactinemia amenorrhea. (Author abstract) (10 Refs)

91. EFFECTS OF RETINOIC ACID ON DIFFERENTIATION OF CHORIOCARCINOMA CELLS IN VITRO.

Chou JY
Pregnancy Res. Branch, Natl. Inst. Child Health and Human Development, NIH, Building 6, Room 128, Bethesda, MD, 20205
J Clin Endocrinol Metab; 54(6):1174-1180 1982

Choriocarcinoma cells maintain multiple hormonal functions in culture. We have found that these cells secreted no immunoreactive pregnancy-specific beta1-glycoprotein (PSbetaG), a placental protein. Choriocarcinoma cells can be induced to synthesize low levels of PSbetaG by retinoic acid, 8-bromo-cAMP (8BrcAMP), cholera toxin, methyl-isobutylxanthine (MIX), and 5-bromo-2'-deoxyuridine (BrdUrd). The simultaneous addition of retinoic acid along with 8BrcAMP, cholera toxin, or MIX gave synergistic induction of PSbetaG. The simultaneous addition of retinoic acid and BrdUrd failed to give even additive induction. In addition to stimulating PSbetaG production, retinoic acid increased the production of hCG and its alpha-subunit (hCGalpha) by choriocarcinoma cells. The simultaneous addition of retinoic acid along with 8BrcAMP, cholera toxin, or MIX gave additive induction for hCG and hCGalpha. Passage of choriocarcinoma cells in medium containing retinoic acid induced a stable altered phenotype characterized by elevated levels of PSbetaG, hCG, and hCGalpha. These retinoid-treated choriocarcinoma cells remained responsive to 8BrcAMP or compounds that increase intracellular cAMP concentrations and to BrdUrd; the production of PSbetaG and hCG was greatly stimulated by 8BrcAMP, cholera toxin, or MIX, and the production of hCG and hCGalpha was greatly inhibited by BrdUrd. However, the production of hCGalpha was only slightly induced by these cAMP modulators, and the production of PSbetaG was not increased by BrdUrd. (Author abstract) (29 Refs)

92. DECREASED RESPONSE TO PHORBOL ESTERS INVOLVES A TWO-STEP PROCESS INCLUDING RECEPTOR MODULATION (MEETING ABSTRACT)

Jaken S, Phillips M, Tashjian AH
Harvard School Public Health, Boston, MA
Toxicologist; 2(1):69 1982

Tumor-promoting phorbol esters (PE) act on cells via interaction with specific membrane receptors. Escape from PE-mediated actions, possibly including tumor promotion, have been documented. We have studied the mechanisms by which cells escape from PE effects using as a model system a clonal strain of mouse pituitary cells (D16) which synthesize and secrete ACTH. PE enhance ACTH release from D16 cells 2-to 5-fold above unstimulated control levels. ED50s for this response, approx 16 nM for phorbol dibutyrate (PDBu), approx 2 nM for phorbol myristate acetate (PMA) agree closely with the apparent Kds of these ligands for the PE receptor as measured by competition for binding with [3H]PDBu. Pretreatment with PE for 2 hr resulted in a decrease in ACTH release with PE rechallenge to 23% of that from cells not pretreated (desensitization). The 2-hr pretreatment did not change the affinity of number of PE receptors nor did it decrease the responsiveness of the cells to other ACTH secretagogues (cAMP, isoproterenol). However, the continued presence of PE caused a gradual decrease in [3H]PDBu binding which was first detected at 5 hr and was maximal by 24 hr. Scatchard analysis indicated a decrease in the number of [3H]PDBu binding sites (down modulation). In these down-modulated cells, the magnitude of PE stimulation of ACTH release correlated well with the number of remaining PE-receptors. (no Refs)

93. ORGANOPHOSPHORUS-INDUCED NEURITE DEGENERATION IN HUMAN NEUROBLASTOMA CELLS (MEETING ABSTRACT)

Graham DG, Abou-Donia MB
Department of Pathology and Pharmacology, Duke University Medical Center, Durham, NC, 27710
Toxicologist; 2(1):109 1982

Human neuroblastoma cells have been developed as an in vitro model for organophosphorus-induced delayed neurotoxicity assuming (1) that neurite degeneration in vitro is analogous to axonal degeneration in vivo, and (2) that reductions in neurotransmitter uptake can serve as quantifiable indices of neurite degeneration. Evidence for neurite degeneration after exposure of LA-N-1 cells to agar-absorbed organophosphorus esters (OP's) has been obtained by electron microscopy. Homogenization and varification of neurite cytosol and swelling of neurite mitochondria were apparent when compared to the cytosol and mitochondria of adjacent cell bodies or with neurites from agar-exposed controls. Reductions in cocaine-inhibitable [3H] norepinephrine uptake occurs after 3 hour exposures of these cells to a variety of OP's, and the reductions follow pseudo-first order kinetics. That the hydrophobic OP's enter the neuroblastoma cells adsorbed to agar was shown in the demonstration that leptophos oxon at 0.5 mM resulted in 16.9% inhibition of [3H] norepinephrine uptake when adsorbed to 6.7 ug of agar/ml, increasing to 31.5% with 67 ug agar/ml and 89.8% with 333 ug agar/ml. Leptophos oxon was alone among leptophos and its phosphorus-containing degredative products in its ability to result in reductions in [3H] norepinephrine uptake, pointing to this metabolite as the ultimate neurotoxin in leptophos-induced delayed neurotoxicity. (no Refs)

94. ROLE OF ENDOGENOUS SUBSTANCES IN CREATION OF THE POOL OF INCREASED RADIORESISTANCE. COMMUNICATION 16. EFFECT OF VARIOUS AET DERIVATIVES IN THE ENDOGENOUS RADIORESISTANCE.

Goncharenko EN, Stoev SV, Graevskaia EE
Faculty Biology, M. V. Lomonosov State Univ., Moscow, USSR
Radiobiologiia; 22(2):252-255 1982

The mechanism of radioprotective effect of 8-aminoethylisothiuronium (AET) derivatives was studied in male albino mice. Administration of adeturon and 2-amino-4-iminothiazoline produced a marked decrease of the level of endogenous radiosensitizers (hydroperoxides of higher unsaturated fatty acids) and the increase of the level of endogenous radioprotectors (serotonin and histamine) in the spleen, small intestine, liver, and stomach of irradiated animals. (8 Refs) (In RUS)

RECEPTOR/ BINDING SITES

95. RAPID TEMPERATURE-DEPENDENT TRANSFORMATION OF THE THYROTROPIN-RELEASING HORMONE-RECEPTOR COMPLEX IN RAT PITUITARY TUMOR CELLS.

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J Biol Chem; 257(10):5462-5470 1982

Thyrotropin-releasing hormone (TRH) binds to specific receptors on GH4C1 rat pituitary tumor cells. The rate of dissociation of [3H]TRH from cell monolayers was much faster (t1/2 less than 1 min) when binding had taken place at 0 C than when binding had taken place at 37 C (t1/2 = 18 min). In isolated membranes the t1/2 values for dissociation were 2 and 26 min after binding at 0 and 23 C, respectively. TRH first formed a complex with rapid dissociation kinetics; the TRH - receptor complex was then converted at elevated temperatures to a form with slow dissociation kinetics. This conversion required 1 hr at 23 C in isolated membranes but was complete within 5 min at 23 to 37 C in intact cells. When [3H]TRH initially bound to cells, 80% of the peptide could be removed by a brief rinse with cold 0.2 M acetic acid/0.5 M NaCl. At 37 C the TRH-receptor complex was transformed to a state where 80% was resistant to the acid/salt rinse within 10 min. This transformation was not reversible and could not be demonstrated in isolated membranes. The rate and extent of conversion of the [3H]TRH-receptor complex to an acid/salt-resistant form were independent of TRH concentration but highly dependent on temperature. Conversion of the TRH-receptor complex was not inhibited by metabolic or cytoskeletal poisons, calcium blockers, lysomotrophic agents, or transglutaminase, protein synthesis, or calmodulin inhibitors. These data suggest that TRH initially binds to a form of the receptor from which the peptide dissociates rapidly. The complex is then converted in a temperature-dependent fashion to a form with slow dissociation kinetics; this can occur in cells or membranes. In intact cells at elevated temperatures, the TRH receptor complex undergoes a further transformation to become acid/salt resistant, and these events all occur within 10 min of hormone binding. (Author abstract) (41 Refs)

96. THYROTROPIN BINDING AND ADENYLATE CYCLASE ACTIVATION IN NORMAL AND NEOPLASTIC HUMAN THYROID TISSUE: LACK OF EFFECT OF THYROGLOBULIN.

Clark OH, Gerend PL, Nissenson RA
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J Clin Endocrinol Metab; 54(6):1157-1163 1982

The effects of bovine TSH (bTSH) and bovine (bTg) and human thyroglobulin (hTg) on the binding of [125I]bTSH and the activation of adenylate cyclase (AC) were studied in both normal and neoplastic human thyroid homogenates in vitro using adenylate cyclase conditions. [125I]bTSH bound specifically and with high affinity to a particulate fraction from normal thyroid and from benign and malignant thyroid neoplasms; this binding was inhibited by unlabeled bTSH (approx Kd = 10.0 mU/ml for normal tissue; Kd = 2.5 mU/ml for thyroid neoplasms). Half-maximal activation of AC was obtained at a TSH concentration of approx 2.5 mU/ml for both normal and neoplastic thyroid tissue, indicating that the high affinity TSH receptors are coupled to AC, at least in the neoplastic thyroid tissue. bTg and hTg did not inhibit [125I]bTSH binding to high affinity TSH receptors in either normal or neoplastic thyroid tissue. bTSH increased AC activity up to 25-fold in neoplastic thyroid tissue and up to 4-fold in normal thyroid tissue, whereas at concentrations up to 1 mg/ml, bTg had no effect. The current study demonstrates that bTSH binds to specific, high affinity receptors and stimulates AC activity in both normal and neoplastic thyroid tissue. bTg and hTg, under the conditions used in this experiment, do not influence TSH binding to its high affinity receptor in these tissues. Since Tg does not influence high affinity TSH binding or AC activity in a particulate fraction rich in plasma membranes from normal or neoplastic thyroid tissue, it is unlikely to have a modulating role on TSH action at the thyroid plasma membrane. (Author abstract) (26 Refs)

97. COVALENT CROSS-LINKING OF A PHOTOACTIVE DERIVATIVE OF CALCITONIN TO HUMAN BREAST CANCER CELL RECEPTORS.

Moseley JM, Findlay DM, Martin TJ, Gorman JJ
Dept. Medicine, Univ. Melbourne, Repatriation General Hosp., Heidelberg, Victoria, 3077, Australia
J Biol Chem; 257(10):5846-5851 1982

A photoaffinity derivative of salmon calcitonin has been produced by transglutaminase-mediated incorporation of N-(beta-aminoethyl)-4-azido-2-nitroaniline into the hormone. The derivative, purified by high pressure liquid chromatography, retained the abilities to bind to cultured T47D breast cancer cells and to stimulate adenylate cyclase in these cells. In both these respects it was equipotent with synthetic salmon calcitonin. Photolysis of the 125I-labeled photoactive salmon calcitonin derivative bound to T47D cells was accompanied by specific labeling to only one component (Mr = 85,000) as assessed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Labeling was observed only upon photolysis and was inhibited by unlabeled synthetic salmon calcitonin but not by the inactive calcitonin analogue, 8-glycine human calcitonin. Reduction did not alter the apparent mol wt of the calcitonin receptor complex. No macromolecular forms of calcitonin were produced by photolysis in the absence of T47D cells. (Author abstract) (29 Refs)

98. CHARACTERIZATION OF INSULIN RECEPTORS IN HUMAN PROMYELOCYTIC LEUKEMIA CELL HL60.

Abita JP, Gauville C, Saal F
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Biochem Biophys Res Commun; 106(2):574-581 1982

The presence of receptors for 125I-insulin on HL60 human promyelocytic leukemia cells with specificity analogous to that observed on mature hemopoietic cells and other human cell types is reported. Half-maximal binding was observed at 20 min incubation. When HL60 cells were incubated with 2 x 10-10M 125I-insulin together with increasing concentrations of nonlabeled insulin for 2 hr, a competitive displacement of labeled insulin was seen. Mean insulin receptor concentration was estimated to be around 45,000 per cell. Porcine and human insulin which have the same biological activity displaced porcine 125I-insulin with the same efficiency while porcine proinsulin which has only 2-5% biological activity was 100 less effective than insulin is displacing 125I-insulin. Neither porcine C-peptide nor porcine glucagon caused measurable displacement of 125I-insulin. These results indicate the presence of specific binding sites for insulin on immature human myeloid cells. Properties of the HL60 insulin receptor resembled those described for other insulin binding cells. (28 Refs)

99. PROGESTIN RECEPTORS IN PROLACTIN AND GROWTH HORMONE PRODUCING TUMOURS IN RATS.

Naess O, Haug E, Attramadal A, Gautvik KM
Inst. Pathology, Rikshospitalet, Oslo, Norway
Acta Endocrinol (Copenh); 100(1):25-30 1982

Progesterone and corticosterone have a similar effect on the production of growth hormone (GH) and prolactin (Prl) by pituitary tumor cells (GH3 cells) in culture. Previously we have shown that progesterone had a high affinity for the glucocorticoid receptors in these cells. Progesterone may therefore exert its effects through binding to the glucocorticoid receptor. The aim of the present study was to investigate if the GH3 tumor cells and an estrogen induced pituitary tumor, which also produce GH and Prl, possess specific receptors for progesterone. Both the GH3 tumors and the estrogen induced pituitary tumor were in fact found to possess cytoplasmatic receptor molecules for progesterone by using the potent progestin R5020 as a marker. Isoelectric focusing revealed one binding component (pH 5.9), which was of protein nature. The binding was of high affinity (KD 2 x 10(-9) mol/l). In the estrogen induced tumor, the maximal binding was 70 fmol/mg cytosol protein. In female rates with GH3 tumors the binding was 55 fmol/mg cytosol protein. Priming of the animals with 1 mg estradiol-valerate increased the binding to 116 fmol/mg cytosol protein, whereas very little binding was found in GH3 tumors from rats castrated 7 days before sacrifice. The receptors in the estrogen induced pituitary tumor and the GH3 tumors exhibited high affinity for R5020 and progesterone, whereas corticosterone had no significant affinity for the receptors. Using exchange assay, it was demonstrated that the cytoplasmic progestin receptors could be translocated to the nucleus after administration of progesterone to the animals. Thus, the presence of specific progesterone receptors, different from the glucocorticoid receptors, strongly indicates that the effects of progesterone on GH and Prl production are mediated through the progesterone receptors. (Author abstract) (21 Refs)

100. PROLACTIN BINDING IN A HORMONE-DEPENDENT AND IN AN ANAPLASTIC SUBLINE OF THE DUNNING R3327 RAT PROSTATIC ADENOCARCINOMA (MEETING ABSTRACT)

Thompson SA, Al-Remaih M, Lubaroff DM, Johnson MP
Departments of Anatomy and Urology, University of Iowa College of Medicine, Iowa City, IA
Anat Rec; 202(3):190A 1982

The growth rate of an androgen-dependent tumor, a subline of the Dunning R3327 rat adenocarcinoma, was studied in normal male, castrated male (Cx), and female rats. The mean tumor volume 104 days following implantation of 3 mm3 subcutaneous piece of tumor was 7340 mm3 in intact males, 254 mm3 in Cx males, and 192 mm3 in females. Tumors grown in intact males lacked glandular structure and exhibited regions of stratified squamous epithelium associated with keratin-like whorls. The immunocytochemical localization of prolactin binding sites in tumors from these three groups was compared with staining in a totally anaplastic, undifferentiated subline of R3327. This anaplastic tumor consisted principally of two populations of cells, ie, clusters of rounded eosinophilic cells interspersed among regions containing many basophilic spindle-shaped cells. Nearly all cells of this tumor were positive for prolactin binding. Binding was present in scattered loci in epithelial cells of tumors from Cx males and females, similar to the pattern described by Witorsch (1979). All three groups exhibited clusters of cells which stained specifically and densely for bound prolactin. These were large cells, closely resembling the densely positive cells of the anaplastic tumor. (no Refs)

101. RECEPTOR BINDING AND PROCESSING OF EPIDERMAL GROWTH FACTOR BY HUMAN BREAST CANCER CELLS.

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J Clin Endocrinol Metab; 55(1):86-93 1982

Epidermal growth factor (EGF) stimulates the growth of human breast cancer cells (MCF-7). To better define the mechanisms for these effects, we studied receptor binding and subsequent processing of [125I]EGF in cells growing in monolayer culture under conditions in which an effect on growth is observed. Binding was temperature dependent and was higher at reduced temperature. At 37 C, binding rapidly reached a maximum (20-60 min) and then gradually decreased. Binding was slower at a reduced temperature. High affinity was demonstrated by the ability of unlabeled EGF to compete for [125I]EGF binding; half maximal displacement was observed at an EGF concentration that also resulted in half-maximal biological activity (1-2 ng/ml). Scatchard plots derived from these data or from those of studies using increasing concentrations of [125I]EGF were curvilinear and superimposable. Plots from binding data obtained at 0 C were also curvilinear, suggesting that the processing and degradation of tracer alone cannot explain this finding. Other peptides did not compete for EGF binding. During a 6-hr incubation, progressive degradation of [125I]EGF occurred on and/or in the cells, with prompt release of low mol wt fragments into the medium. Furthermore, during this time, the bound intact EGF became more resistant to dissociation by excess unlabeled EGF. Reduced binding (50%), not due to simple occupancy, was also noted during a 2-hr preincubation with unlabeled EGF, indicating down-regulation of receptor. These data suggest the following sequence of events. At 37 C, EGF rapidly binds to specific receptors on MCF-7 cells. The bound EGF becomes more and more difficult to dissociate from the cell, and the number of available receptors is reduced, implying sequestration in the cell membrane and/or internalization of the hormone-receptor complex. Gradually, EGF is degraded, and the products are released from the cell. Human breast cancer appears to be a target for EGF action. (Author abstract) (24 Refs)

102. EFFECTS OF DIETARY LIPIDS ON LACTOGENIC HORMONE RECEPTOR BINDING IN RAT MAMMARY TUMORS.

Cave WT, Erickson-Lucas MJ
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JNCI; 68(2):319-324 1982

Both epidemiologic studies in humans and experiments in laboratory animals have indicated that high-fat (HF) diets promote mammary tumor growth; however, the biochemical mechanisms responsible for this accelerated tumor growth are poorly understood; thus this study was designed to determine whether diet-induced alterations in the lipid composition of mammary tumor cell membranes were associated with differences in lactogenic hormone binding capacity. Mammary tumors were induced with N-methyl-N-nitrosourea in 50-day-old female inbred Buffalo rats that were maintained on either HF or low-fat (LF) diets composed of either 20% corn oil or 0.5% corn oil, respectively. The microsome-membrane fractions of these tumors were then analyzed for specific lactogenic hormone binding with the use of 125I-labeled human growth hormone. Methylated extracts of these same membrane fractions were also subjected to gas-liquid chromatography. Our results demonstrated that the mammary tumor membranes of the HF group did have a significantly greater lactogenic binding capacity than those of the LF group and that these differences in hormone binding were accompanied by significant alterations in the membrane qualitative fatty acid profiles of each group. Therefore, one way in which dietary lipids may be able to influence mammary tumor growth is by modification of the lactogenic hormone binding capacity of tumor cell membranes. (Author abstract) (27 Refs)

103. SEROTONIN STORAGE POOLS IN BASOPHIL LEUKEMIA AND MAST CELLS: CHARACTERIZATION OF TWO TYPES OF SEROTONIN BINDING PROTEIN AND RADIOAUTOGRAPHIC ANALYSIS OF THE INTRACELLULAR DISTRIBUTION OF [3H]SEROTONIN.

Tamir H, Theoharides TC, Gershon MD, Askenase PW
Div. Neuroscience, New York State Psychiatric Inst., New York, NY, 10032
J Cell Biol; 93(3):638-647 1982

We studied binding of serotonin to protein(s) derived from rat basophil leukemia (RBL) cells and mast cells. We found two types of serotonin binding protein in RBL cells. These proteins differed from one another in mol wt and eluted in separate peaks from sephadex G-200 columns. Peak I protein (KD = 1.9 x 10(-6) M) was a glycoprotein that bound to concanavalin A (Con A); Peak II protein (KD1 = 4.5 x 10(-8) M; KD2 = 3.9 x 10(-6) M) did not bind to Con A. Moreover, binding of [3H]serotonin to protein of Peak I was sensitive to inhibition by reserpine, while binding of [3H]serotonin to protein of Peak II resisted inhibition by that drug. Other differences between the two types of binding protein were found, the most significant of which was the far more vigorous conditions of homogenization required to extract Peak I than Peak II protein. Neither Peak I nor Peak II protein resembled the serotonin binding protein (SBP) that is found in serotonergic neurons of the brain and gut. Electron microscope radioautographic analysis of the intracellular distribution of [3H]serotonin taken up in vitro by RBL cells or in vivo by murine mast cells indicated that essentially all of the labeled amine was located in cytoplasmic granules. No evidence for a pool in the cytosol was found and all granules were capable of becoming labeled. The presence of two types of intracellular serotonin binding proteins in these cells may indicate that there are two intracellular storage compartments for the amine. Both may be intragranular, but Peak I protein may be associated with the granular membrane while Peak II protein may be more free within the granular core. Different storage proteins may help to explain the differential release of amines from mast cell granules. (Author abstract) (36 Refs)

104. INSULIN, GLUCAGON, AND SOMATOSTATIN RECEPTORS ON CULTURED CELLS AND CLONES FROM RAT ISLET CELL TUMOR.

Bhathena SJ, Oie HK, Gazdar AF, Voyles NR, Wilkins SD, Recant L
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Diabetes; 31(6,part1):521-531 1982

Insulin, glucagon, and somatostatin binding were studied on rat parent rat islet-cell cultures and insulin- and somatostatin-secreting clones derived from them. Non-insulin- secreting somatostatin clones and low insulin- secreting clones showed significantly greater insulin binding (8.7% and 7.4%, respectively) than either insulin-secreting clones or parent cells (4-5%). These findings suggest that down regulation of the insulin receptor may have occurred. True glucagon receptors were demonstrated on all cells, but the somatostatin clones had 2-4x as many sites as the other cells tested, although the affinity was markedly reduced. Somatostatin secreting cells (parent and somatostatin clones) bound 2.59% versus 1.24% for all non-somatostatin-secretors. Preincubation experiments with parent cells showed down regulation of somatostatin binding, but somatostatin-secreting cells exhibited enhanced somatostatin binding during incubation. Receptors for insulin, glucagon, and somatostatin evidently are present on parent islet-cell tumor cells and in all clones examined, but binding degradation and hormone secretion make quantitation of receptors impossible. Characteristic binding patterns exist, however, only for insulin-secreting vs somatostatin-secreting clones. (45 Refs)

105. ADRENERGIC RECEPTORS IN HUMAN AND EXPERIMENTAL PHEOCHROMOCYTOMA.

Snavely MD, Motulsky HJ, O'Connor DT, Ziegler MG, Insel PA
Dept. Medicine, Univ. California, San Diego, La Jolla, CA, 92093
Clin Exp Hypertens [A]; 4(4/5):829-848 1982

Work characterizing alpha-adrenergic receptors on human platelets and on rat renal cortical membranes is reviewed, and results of studies of these receptors from patients and rats with pheochromocytoma are reported. Subtype-selective radioligands were used to study alpha1 (3H-prazosin) and alpha2 (3H-yohimbine) receptors in human platelets and rat renal cortical membranes. The number of yohimbine binding sites on platelets was unaltered by 4 or 24 hr incubations with 0.1 milliM epinephrine. In vitro incubation with epinephrine at concentrations which vastly exceeded physiological and even pathological plasma concentration also did not down regulate platelet alpha2-adrenergic receptors. The number of alpha2-adrenergic receptors on platelets of five patients with pheochromocytoma exposed to chronically high levels of catecholamines, remained normal as well. An animal model of pheochromocytoma is discussed. In rats with pheochromocytoma down regulation of beta- and alpha1-adrenergic receptors was demonstrated. Experimental pheochromocytoma is a useful model system for exploring down regulation of these receptor populations. (45 Refs)

106. DIFFERENCES IN THE HORMONAL STIMULATION OF NORMAL AND LEUKEMIC HUMAN PERIPHERAL LEUKOCYTES (MEETING ABSTRACT)

Paietta E, Schwarzmeier JD
First Medical Department, University of Vienna, Vienna, Austria
12th Workshop on Leukocyte Cultures, February 14-17, 1982, Vienna, Austria Wierner Medizinische Akademie; :A69 1982

We have measured the density of beta-adrenoceptors and the stimulation of adenylate cyclase (AC) by the beta-adrenergic agonist isoproterenol (INE), prostaglandin E1 (PGE1) and histamine (HIS) in normal as well as leukemic leukocytes. The number of beta-adrenoceptors on intact cells was determined using the beta-adrenergic antagonist 125I-iodohydroxybenzylpindolol (IHYP) as radioligand. One single class of high affinity binding sites for IHYP was identified on normal lymphocytes, monocytes and polymorphonuclear leukocytes (PMN). Maximal binding of IHYP, ie the quantity of beta-adrenoceptors present did not differ significantly among normal leukocytes. Fractionation of lymphocytes into B- and T-cells revealed significantly higher beta-receptor numbers on B than on T cells. Among leukemic cells tested, blast cells from AMOL (acute monocytic leukemia) and AMMOL (acute myelomonocytic leukemia) patients usually exhibited much higher beta-receptor densities than those from AML (acute myelocytic leukemia), and beta-receptor numbers were lowest in CLL (chronic lymphocytic leukemia) and ALL (acute lymphocytic leukemia). AC activity measured as cyclic adenosine 3', 5' - monophosphate (cAMP) produced per mg protein per min was studied in cell membrane preparations. Despite the fact that beta-receptors numbers were comparable in lymphocytes, monocytes and PMN, the latter showed a much weaker response to INE, but also to PGE1 and HIS. Results obtained using GTP and NaF as positive effectors of AC indicate that the poor hormonal responsiveness of PMN might be due to an impaired coupling between hormone receptors and catalytic unit of AC. Normal B lymphocytes showed a marked increase in cAMP production upon stimulation with INE, whereas T cells failed to respond. This relates to the different numbers of receptors identified on the two cell types. Among leukemic cells, the effectiveness of INE to stimulate AC corresponded to the beta-receptor numbers found to be present. AC reactivity to PGE1 and HIS followed the pattern of response to INE. (no Refs)

OTHER RELATED STUDIES

107. INDUCTION OF ALKALINE PHOSPHATASE AND THE GLYCOPROTEIN HORMONE ALPHA SUBUNIT IN HELA CELLS BY INHIBITORS OF DNA POLYMERASE.

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Arch Biochem Biophys; 216(1):234-246 1982

Effects of two eukaryotic DNA polymerase inhibitors, aphidicolin (ApH) and phosphonoformic acid (PFA) on synthesis of placental alkaline phosphatase (PAP) and of the glycoprotein hormone alpha subunit in Hela cells were investigated. Both ApH (1.0-5.0 ug/ml) and PFA (1.2 or 3.8 milliM) inhibited DNA synthesis almost completely (82-93%), even at the lowest concentrations tested. Both inhibitors were good inducers of both PAP and the glycoprotein hormone alpha subunit. PAP activity was enhanced 60-100% by ApH at 1 ug/ml, and alpha subunit levels were increased 5-fold at an ApH concentration of 5 ug/ml. PAP activity showed a 7-to 8-fold increase and alpha subunit and a 2-to 3-fold increase as PFA concentration was increased to 3 milliM. Partial characterization of induced alpha subunit and PAP activity suggested that they are similar to the uninduced proteins. ApH (2.ug/ml) and PFA (2.5 milliM) acted synergistically with butyrate (3 milliM) but not with hydroxyurea (1 milliM). The fact that the concentration of ApH required to produce a half-maximal induction of the alpha subunit (15 ug/ml) was of an order of magnitude higher than the concentration required to inhibit DNA synthesis by 50% (0.1 ug/ml) makes it unlikely that a direct relation exists between protein induction and DNA synthesis inhibition. (53 Refs)

108. CANCER ETIOLOGY: CURRENT STATES OF OUR KNOWLEDGE (MEETING ABSTRACT)

Thomas DB
No affiliation given
Fifth Annual Snohomish County Cancer Conference, February 11, 1982, Everett, Washington Snohomish County Medical Education Board; 1982

The environmental causes of cancer (known and suspected) are: A) chemicals - tobacco smoke, alcohol, industrial exposures, and drugs; B) radiation - ionizing and non-ionizing; C) exogenous hormones - transplacental exposures, oral contraceptives, menopausal estrogens, and others; D) infectious agents - viruses and others; and E) dietary factors - deficiencies, excesses, and contaminants. (no Refs)

109. CIRCULATING PLACENTAL PROTEINS (HCG, SP1 AND PP5) IN TROPHOBLASTIC DISEASE.

Lee JN, Salem HT, Chard T, Huang SC, Ouyang PC
Dept. Obstretics and Gynecology and Reproductive Physiology, St. Bartholomew's Hosp. Medical Coll, London, England
Br J Obstet Gynaecol; 89(1):69-72 1982

Serum human chorionic gonadotrophin (hCG), pregnancy-specific beta1-glycoprotein (SP1) and placental protein 5 (PP5) levels have been measured by radioimmunoassay in 20 patients (116 samples) with hydatidiform mole, 1 patient (9 samples) with invasive mole and 10 patients (103 samples) with choriocarcinoma. Measurement of both serum SP1 and hCG are useful in the monitoring of these diseases. The presence of PP5 in hydatidiform mole and its absence in choriocarcinoma support the hypothesis that PP5 is closely associated with the invasive activity of malignant trophoblast. (Author abstract) (15 Refs)

110. EXPERIMENTAL INDUCTION OF C CELL TUMOURS IN THYROID BY INCREASED DIETARY CONTENT OF VITAMIN D3.

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Acta Endocrinol (Copenh); 100(1):41-45 1982

Neonatal Wistar rats were given either 0, 5 or 10 uCi 131I within 24 hr of birth. Following weaning, they were fed a diet high, normal or deficient in vitamin D, for up to 2 yr. Animals were sacrificed at approx 3 monthly intervals, and serial sections of thyroid scanned for C cell tumors following calcitonin localization. Plasma calcium levels were also measured, and all results statistically analyzed. As expected, those animals given the high vitamin D had significantly raised calcium levels over those on a normal D diet, whilst those given a low D diet had lower calcium levels than normal. Analysis of the incidence of C cell tumors showed that those given a high D diet had significantly more C cell tumors, whilst those on a low D diet had significantly fewer than normal. Radiation dose also influenced C cell tumor incidence. There was a significant relationship between the vitamin D content of the diet and the incidence of C cell tumors, with those animals on a high D diet having the largest number of tumors. It is suggested that vitamin D or its metabolites may directly promote C cell growth, and that the high incidence of C cell tumors in the normal laboratory rat reflects the artificially high vitamin D content of the laboratory rat diet. The dietary vitamin D content may also be relevant to the variation in geographical incidence of medullary carcinoma in man. We consider it likely that vitamin D metabolites may play a significant role in the control of C cell function, hyperplasia and tumor formation in the rat, and that this may be more important in tumor formation than the role of serum calcium variation. (Author abstract) (20 Refs)

111. PRESENCE OF CALMODULIN IN PARATHYROID ADENOMAS.

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Miner Electrolyte Metab; 7(5):273-280 1982

A significant percent of parathyroid adenomas demonstrate decreased sensitivity to the suppressive effects of calcium on parathyroid hormone secretion. The recognition that calmodulin mediates a large number of calcium-dependent cellular events suggests that calmodulin may play a key role in the normal regulation by calcium of parathyroid activity. We therefore undertook to determine if parathyroid adenomas contained calmodulin and if so, if the calmodulin content of adenomas could be correlated with the serum concentrations of calcium and immunoreactive parathyroid hormone (IPTH) in hyperparathyroid patients prior to surgery. Calmodulin was assayed by activation of a calmodulin-stimulatable phosphodiesterase (PDE) obtained from rat brain. We found PDE-stimulating activity in each of sex adenoma extracts examined. The stimulation had the following properties, which are characteristic of calmodulin-mediated processes: (1) it required the presence of calcium; (2) the dose response to adenoma extract and human red blood cell calmodulin were parallel, and (3) the stimulation was phenothiazine-inhibitable . The amount of calmodulin present in the adenoma extracts ranged from 0.4 to 1.25 units/ug protein. No correlation was found between the calmodulin content of the adenomas and the presurgical levels of either serum calcium or serum IPTH. (Author abstract) (31 Refs)

112. PITUITARY ADENOMAS.

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Oncologic 12: 197 pp., 1981.

Pituitary adenomas are discussed and in three sections the following are included: a 'self-instructional text' which features answers and comments to specific questions asked in the text, a 'study guide' with spaces for the reader to write responses, and a 'post-test' unit for the reader to send in for grading and receive continuing education credits. The main presentation consists of many figures, graphs, radiographs, and photographs related to the areas treated: acromegaly, Cushing's disease, prolactin-secreting tumors, tumors due to mass effects, and craniopharyngiomas. Some areas reviewed for acromegaly include clinical presentation, work-up procedures, radiographic presentation, anatomy and physiology, incidence and etiology, staging, and various forms of treatment. Some areas treated with regard to prolactin-secreting tumors includes surgical treatment, 'empty sella', and radiation therapy. The self-instructional and self-evaluation portions of the book are designed to help the reader to examine his decision-making ability as regards pituitary tumors. (105 Refs)

113. MODEL OF MIXED MULTIPLE ENDOCRINE NEOPLASIA IN THE LONG-EVANS RAT (MEETING ABSTRACT)

Lee AK, DeLellis RA, Wolfe HJ
Department of Pathology, Tufts University School of Medicine and the New England Medical Center, Hospital Boston, MA
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

In human kindreds with multiple endocrine neoplasia (MEN) syndromes, concomitant thyroidal C cell, adrenal medullary and parathyroid proliferative lesions are found in type II phenotype patients, whereas pituitary, pancreatic islet, and parathyroid abnormalities develop in patients with type I phenotype. Examples of overlap between the two syndromes are rare. In contrast, in the aging Long-Evans rat strain concomitant spontaneous thyroidal C cell, adrenal meduallary and pituitary proliferative abnormalities are common findings. The incidence of these abnormalities increased with age in a colony of male Long-Evans rats maintained in our laboratory for more than 3 years. In 24-to 36-month-old animals, 44 per cent harbored thyrodial nodular C cell hyperplasia and/or medullary thyroid carcinoma, 31 per cent developed adrenal medullary nodular hyperplasia, and 50 per cent exhibited anterior pituitary nodules. In the pituitary, immunohistochemistry revealed that the majority of the nodules contained prolactin, whereas a few contained immunoreactive thyrotropin, adrenocorticotropin, and gonadotropins. Ultrastructurally, most of the nodules displayed characteristics described for sparsely granulated prolactinomas. Quantitative studies indicated a progressive diffuse increase in prolactin cells with age. The nodular lesions in the thyroid, pituitary, and adrenal medulla were frequently multiple and developed on a background of diffuse hyperplasia seen in all the old animals. (no Refs)

114. TAMOXIFEN INHIBITS LEYDIG CELL STEROIDOGENESIS: IN VIVO AND IN VITRO STUDIES.

Lin T, Murono EP
Medical Service, William Jennings Bryan Dorn Veterans Hosp., Columbia, SC, 29201
Metabolism; 31(6):543-547 1982

The effects and mechanism of action of tamoxifen (TAM) on steroidogenesis in Leydig cells of mature Sprague-Dawley rats were investigated. Hypophysectomized rats were treated with 0, 10, or 100 ug TAM suspended on 0.1 ml corn oil. Twenty-four hr later, tail blood samples were obtained, followed by administration of 5 units/100 g body wt human chorionic gonadotropin (HCG) sc. Two hr later, rats were sacrificed, trunk blood collected, and sera separated and stored. TAM in a dose of 10 ug had no effect on HCG-stimulated testosterone in 21 day old hypophysectomized rats formation, while 100 ug TAM did reduce HCG-stimulated testosterone synthesis significantly. TAM had no effect upon basal testosterone levels in 60 day old hypophysectomized rats. After HCG stimulation, there was a 46% reduction in mean plasma testosterone levels in rats treated with 10 ug TAM and 69% reduction in rats treated with 100 ug TAM. When decapsulated testes from these rats were incubated for 3 hr, rats treated with 100 ug TAM produced significantly less testosterone when compared to rats treated with either 10 ug TAM or controls. TAM thus directly inhibits testosterone response to gonadotropin stimulation both in immature and mature hypophysectomized rats. Conversion of pregnenolone to testosterone was blocked by TAM. Both estrogen and TAM inhibited leuteinizing hormone-stimulated testosterone formation, but with different patterns of inhibition. TAM had no effect upon HCG binding to gonadotropin receptors, or upon adenylate cyclase activity. These results indicate that TAM blocks multiple steps in steroidogenesis. (29 Refs)

115. ESTABLISHMENT AND CHARACTERIZATION OF TWO NEOPLASTIC CELL LINES (U-1285 AND U-1568) DERIVED FROM SMALL CELL CARCINOMA OF THE LUNG.

Bergh J, Larsson E, Zech L, Nilsson K
Wallenberg Lab., Univ. Uppsala, Box 652, 751 22 Uppsala, Sweden
Acta Pathol Microbiol Scand [A]; 90(3):149-158 1982

Two human cell lines have been established in vitro from patients with small cell carcinoma of the lung (SCC). The U-1285 line was derived from the classical small cell type of SCC while the U-1568 originated from a larger cell variant. The cell lines grow as suspension cultures and have been passaged continuously in vitro for 3 yr (U-1285) and 2 yr (U-1568), respectively. The malignant nature of the lines is suggested by their infinite growth potential, their capacity to form colonies in agarose and their aneuploidy. Both cell lines contain cytoplasmic electron dense particles indistinguishable from classical neurosecretory granules but only in U-1568 has hormone production (human chorion gonadotropin (alpha-HCG)) been proven. The U-1568 line produces carcino-embryonic antigen (CEA) while both U-1285 and U-1568 produce alpha-feto-protein (AFP). Chromosome analysis reveal aneuploidy of both lines. Among structural aberrations, involvement of chromosome 14 in U-1285 and chromosomes 1, 7 and 12 in U-1568 is interesting since alterations of these chromosomes have been described previously in other malignant conditions. (Author abstract) (44 Refs)

116. A STUDY OF THE GROWTH REQUIREMENTS OF HUMAN TUMOUR CELLS IN TISSUE CULTURE.

Rowbottom LA, Whitehead RH, Roberts GP, Hughes LE
(c/o Hughes) Univ. Dept. Surgery, Welsh Natl. Sch. Medicine, Heath Park, Cardiff CF4 4XN, Wales
Aust J Exp Biol Med Sci; 59(1):91-100 1981

The effect of potential growth enhancing substances and other environmental factors on the growth of human cells in culture were examined. For all the cell lines tested the optimum pH range was 7.45-7.55. Optimum osmolality varied with different cell lines, optimum values being 240 milliosmoles/kg for melanoma cell lines and fetal fibroblasts, 260 milliosmoles/kg for adult fibroblasts and 300 milliosmoles/kg for a breast cancer cell line. A number of hormones were found to affect the growth of the cell lines examined. Insulin and hydrocortisone enhanced the growth of all the tumor cells tested, whereas 17 beta-estradiol enhanced the growth of breast cancer cells but inhibited the growth of melanoma cells and fibroblasts. Stilbestrol inhibited the growth of all the cell lines but prolactin enhanced the growth of melanoma cells and inhibited fibroblast cell growth. Addition of galactose to the medium stimulated the growth of all cell lines tested, whereas sucrose and fructose resulted in stimulation of tumor cell growth but had little effect on fibroblasts. Alpha-thioglycerol and beta-mercaptoethanol enhanced the growth of the tumor cells but had little effect on the growth of fibroblasts. A modified medium has been formulated which enhanced the growth of all the cell lines used when compared with McCoy's 5A medium. (Author abstract) (19 Refs)

117. DISCORDANT CORTISOL RESPONSE TO EXOGENOUS ACTH AND INSULIN-INDUCED HYPOGLYCEMIA IN PATIENTS WITH PITUITARY DISEASE.

Borst GC, Michenfelder HJ, O'Brian JT
Endocrinology Branch, Natl. Naval Medical Center, Bethesda, MD, 20814
N Engl J Med; 306(24):1462-1464 1982

It has been suggested that the iv response to ACTH accurately predicts the integrity of the hypothalamic-pituitary-adrenocortical (HPA) axis without causing the side effects due to insulin-induced hypoglycemia. However, the short ACTH stimulation test in four patients with pituitary tumors failed to reveal abnormalities of the HPA axis that were demonstrated by the insulin-tolerance test. (11 Refs)

118. SOMATOSTATIN AS A MARKER FOR CARCINOID TUMORS: AN IMMUNOHISTOCHEMICAL AND ULTRASTRUCTURAL STUDY (MEETING ABSTRACT)

Dayal Y, O'Briain DS, Nunnemacher G, DeLellis RA, Wolfe HJ, Reichlin S
Department of Pathology, Tufts University School of Medicine, Boston, MA
Lab Invest; 46(1):17A 1982

Somatostatin (SRIF), a hormone that inhibits the release of a number of polypeptide hormones, is produced by the D cells that are dispersed throughout the mucosa of the gastrointestinal tract from stomach to rectum. Carcinoid tumors, arising from the various endocrine cell types in the gastrointestinal mucosa, are known to elaborate a wide variety of polypeptide hormones that are produced by their normal counterparts. Forty 'hormonally silent' carcinoid tumors from various intestinal and extraintestinal locations were, therefore, studied immunocytochemically for the presence of SRIF and other polypeptide hormones to determine whether localization of a particular hormone within the tumor cells might serve as a marker for tumor of a given anatomical site. Although 25 tumors showed immunoreactivity for one or more hormones, SRIF was the hormone most frequently encountered (16 cases). In two duodenal carcinoids, strong immunoreactivity for SRIF was seen in virtually all of the tumor cells. Immunoelectron microscopic studies localized SRIF to secretory granules averaging 475 nm in diameter. In the remaining cases, SRIF positivity was usually present in a smaller subpopulation of cells dispersed focally throughout the tumor. When correlated with the anatomical location of these tumors, somatostatin was demonstrated in five of five foregut, four of seven hindgut, and four of nine extraintestinal carcinoids. In contrast, SRIF could be localized in only three of 19 midgut tumors. (no Refs)

119. SYSTEMIC MANIFESTATIONS OF GUT MALIGNANCY.

Bartholomew LG, Schutt AJ
Mayo Medical Sch., Mayo Clinic and Mayo Foundation, Rochester, MN, 55901
Gastrointestinal Cancer 1. Decosse JJ and Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

Manifestations of gut malignancy are reviewed by body system affected, including dermatologic (acanthosis nigricans, dermatomyositis, nodular fat necrosis, tylosis, genetic disorders), cardiovascular, hematologic (anemia, erythrocytosis, leukocytosis, thrombocytosis, thrombocytopenia, coagulation defects, immunologic disorders), endocrine and metabolic manifestations (islet cell, malignant carcinoid, ectopic hormone syndromes), neuromuscular, rheumatologic, renal, and gastrointestinal. (139 Refs)

120. STIMULATION OF PHAGOCYTOSIS BY A T CELL LYMPHOMA-DERIVED LYMPHOKINE (MEETING ABSTRACT)

Simrell CR, Crabtree G, Cossman J, Fauci AS, Jaffe ES
National Institutes of Health, Bethesda, MD
Lab Invest; 46(1):77A 1982

Certain patients with peripheral T cell lymphoma develop a syndrome that mimics malignant histiocytosis (MH). This phenomenon may involve a lymphokine produced by neoplastic T cells that can stimulate phagocytic cells. To test this hypothesis, neoplastic cells from patients with malignant lymphomas were cultured and supernatants were tested for the presence of a phagocytosis-inducing factor (PIF) using the macrophage-like cell line U937. Phagocytosis was assayed using IgG-coated OX-RBC. Fc receptors on U937 cells were measured by binding of 125I-IgG. Control studies showed PIF activity in supernatants from normal peripheral blood mononuclear cells (MNC) activated in mixed leukocyte culture (MLC) or by Concanavalin A; unstimulated supernatants were negative. MLC supernatants also induced an increase in Fc receptors. Supernatants from the concanavalin A-stimulated cultures did not. Supernatants from two of 13 patients with malignant lymphomas of T cell origin also contained PIF activity. One of these two patients died with the MH-like syndrome. A supernatant from one case of T cell acute lymphoblastic leukemia was also positive. None of these supernatants induced any increase in Fc receptors. Supernatants from 11 cases of non-Hodgkin's disease were negative for PIF. Two lymph nodes with reactive follicular hyperplasia and two normal spleens also failed to yield any activity, although MNC from a reactive pleural fluid containing 50 per cent T cells did. (no Refs)

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CHARACTERIZATION OF NON-STEROID HORMONES IN EXPERIMENTAL AND IN VITRO SYSTEMS

1. ALTERNATIVE RNA PROCESSING IN CALCITONIN GENE EXPRESSION GENERATES MRNAS ENCODING DIFFERENT POLYPEPTIDE PRODUCTS.

Amara SG, Jonas V, Rosenfeld MG, Ong ES, Evans RM

Div. Endocrinology, Sch. Medicine, Univ. California, San Diego, La Jolla, CA, 92093

Nature; 298(5871):240-244 1982

Alternative processing of RNA transcripts from the calcitonin gene results in the production of distinct mRNAs encoding the hormone calcitonin or a predicted product referred to as calcitonin gene-related peptide (CGRP). The calcitonin mRNA predominates in the thyroid while the CGRP-specific mRNA appears to predominate in the hypothalamus. These observations lead us to propose a model in which developmental regulation of RNA processing is used to increase the diversity of neuroendocrine gene expression. (Author abstract) (34 Refs)

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HE 20. 3173/2:

2. DIRECT EVIDENCE FOR THE 'THYROID DEPENDENCE' OF HEPATOMA CELLS GROWN IN CULTURE (MEETING ABSTRACT).

Solomon DH, Mishkin S
Royal Victoria Hospital and McGill University Clinic, Montreal, Quebec, Canada
Gastroenterology; 82(5,part2):1258 1982

We have demonstrated that the local and metastastic growth of Morris Hepatoma (MH) number 44 is 'thyroid dependent'. Cell cultured prepared from HM number 44 and host liver were grown successfully for 8 days in Ham's F12 media containing 10% fetal calf serum (FCS). Daily determinations of cell number and thymidine kinase activity were performed. Depletion of iodothyronines from the incubation medium inhibited the growth of liver and hepatoma cells by 16% and 37% respectively, while maximun inhibition of thymidine kinase activities were 50% and 60% respectively. Addition of triiodothyronine (T3) (200nM) to the T3 depleted medium increased the number of liver and hepatoma cells by sixty-two percent and 83% respectively and the activity of thymidine kinase by 65% and 83% respectively. Although the addition of T3 (200nM) to 'euthyroid' FCS increased thymidine kinase activity by 19-44%, cell numbers did not increase by more than 15% in cultures of liver and MH number 44. This study documents for the first time that the growth of hepatoma cells is directly affected by thyroid status, and confirms our in-vivo observation that hepatoma cells are more sensitive than are liver cells. (3 Refs)

3. SIMULTANEOUS DETECTION OF THYROGLOBULIN (TG), THYROXINE (T4), AND TRIIODOTHYRONINE (T3) IN NONTOXIC THYROID TUMORS BY THE IMMUNOPEROXIDASE METHOD.

Kawaoi A, Okano T, Nemoto N, Shiina Y, Shikata T
Dept. Pathology, Yamanashi Medical Sch., 1110 Shimokato, Tamaho-mura, Nakakoma-gun, Yamanashi-ken 409-38, Japan
Am J Pathol; 108(1):39-49 1982

In 97 nontoxic thyroid tumors, detection of thyroxine (T4), and triiodothyronine (T3) was attempted by the immunoperoxidase method. T4 was demonstrated in 58 tumors (59.8%) and T3 in 76 (78.4%). The feasibility of biosynthesis of T4 and T3 by such tumors was thus established. In 65 of the tumors, we applied the immunostaining method to serial or semiserial sections to study the correlation among the localizations of thyroglobulin(Tg), T4, and T3. The localization of T4 agreed relatively well with that of Tg, and part of the Tg-positive structure frequently revealed simultaneous positive staining for T4. The localization of T3, however, did not always correspond with that of T4 or Tg. T4 and T3 with localizations identical to that of Tg may be considered to be bound to Tg, but the mode of existence of T3 without correspondence in localization to Tg remains unknown. (Author abstract) (34 Refs)

4. DESIGN AND SYNTHESIS OF STRUCTURAL, STEREOISOMERIC AND CONFORMATIONALLY-RESTRICTED ANALOGUES OF ALPHA-MELANOTROPIN: COMPARATIVE BIOLOGICAL PROPERTIES ON MELANOPHORES AND MELANOMA CELLS.

Sawyer TK
The University of Arizona, Tucson, AZ
Diss Abstr Int [B]; 42(11):4431-B 1982

Several chemically-modified analogs of alpha-melanotropin (alpha-MSH, Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val NH(2)) were prepared by solid-phase peptide synthesis, including [Nle4]-alpha-MSH, Ac-[Nle4]-alpha-MSH4-13-NH2, Ac-[Nle4]-alpha-MSH1-6-NH2, Ac-alpha-MSH7-10-NH2, Ac-alpha-MSH11-13-NH2, Ac[Nle4]-alpha-MSH4-10-NH2, Ac-[Nle4,D-Phe7]-alpha-MSH4-10-NH2, [Nle4,D-Phe7]-alpha-MSH, Ac-alpha-MSH4-10-NH2,Ac-[Tyr4]-alpha-MSH4-10-NH2 and [half-Cys4, half-Cys10]-alpha-MSH. A comparative biological analysis in vitro of these analogs on several different vertebrate pigment cell systems provided the following results: (1) The [Nle4, D-Phe7]-alpha-MSH effected high melanotropic potency, ultralong biological activity and unprecedented metabolic stability. (2) Utilizing [Nle4, D-Phe7]-alpha-MSH as a molecular probe, two melanotropic receptor types were demonstrated which were mechanistically different in terms of calcium dependency and apparent hormone-receptor complex reversibility. (3) The Ac-[Nle4, D-Phe7]-alpha-MSH4-10-NH2 was a highly potent active site (Met-Glu-His-Phe-Arg-Trp-Gly) analog of alpha-MSH without the ultralong melanotropic activity possessed by the parent stereostructural tridecapeptide. (4) The [half-Cys4, half-Cys10]-alpha-MSH exhibited superpotency on frog (Rana pipiens) melanophores and provided experimental evidence that a pseudocyclic conformation of the native hormone containing a beta-turn structural requirement at His-Phe-Arg-Trp might be related to its biological activity at the pigment cell receptor. The [Nle4, D-Phe7]-alpha-MSH may be suitable for use as a radio-labeled tracer or drug-delivery agent for the localization or treatment of human melanoma in vivo. (no Refs)

5. CELL COMPETENCE FOR INDUCTION OF DIFFERENTIATION BY INSULIN AND OTHER COMPOUNDS IN MYELOID LEUKEMIC CLONES CONTINUOUSLY CULTURED IN SERUM-FREE MEDIUM.

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Blood; 60(1):208-212 1982

Clones of myeloid leukemic cells varying in their competence for induction of differentiation have been continuously grown in serum-free medium. In the medium used, which contained transferrin, the growth rates of these cells were nearly similar to those found in serum-containing medium. The clones also maintained in this medium their competence for induction of differentiation by the normal macrophage and granulocyte differentiation-inducing protein MGI-2, the steroid dexamethasone, and lipopolysaccharide. In contrast to the results with these inducers, some clones continuously cultured in a serum-free medium showed a gain of inducibility by insulin and another clone a gain of inducibility by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate in low serum and serum-free medium. Induction of differentiation by these two compounds was therefore inhibited in these clones by the presence of serum. It is suggested that serum-free medium may also show the existence of other inducers of differentiation not detected in serum-containing medium and that these results are relevant to the possible therapeutic use of compounds such as insulin for the induction of normal differentiation in leukemic cells in vivo. (Author abstract) (24 Refs)

6. EFFECT OF GUCAGON ON AMINO ACID TRANSPORT AND CYCLIC ADENOSINE 3':5'-MONOPHOSPHATE PRODUCTION IN RAT HEPATOMA CELL LINE MCA-RH 8994 IN CULTURE.

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Cancer Res; 42(8):3116-3119 1982

The rates of alpha-aminoisobutyrate (AIB) transport and cyclic adenosine 3':5'-monophosphate (cAMP) production in response to glucagon (2 x 10(-7) M) have been determined in monolayer cultures of hepatoma cell line 8994 (refes to hepatoma cell line McA-RH 8994) under three different calcium treatments. The calcium treatments were: (a) control, cultures maintained in calcium-containing medium without prior calcium depletion; (b) calcium depleted, cultures maintained in calcium-free medium after treatment with ionophore A23187 and ethylene glycol bis(beta-aminoethyl ether)-N,N'-tetraacetic acid; (c) calcium repleted, cultures maintained in calcium-containing medium after treatment with A23187 and ethylene glycol bis (beta-aminoethyl ether)-N,N'-tetraacetic acid. In the control cultures, glucagon in the absence of methylisobutylxanthine (MIX) has no effect on the rate of AIB transport. AIB transport is approx doubled when glucagon is added in the presence of MIX. Calcium depletion and calcium repletion enhance the rate of AIB transport by about 50 and 100%, respectively. Glucagon and N6,O2-dibutyryl cyclic adenosine 3';5'-monophosphate (1 x 10(-4) M) further increase the rate of AIB transport by 10% in calcium-depleted cultures and by 50% in calcium-repleted cultures. The stimulation of AIB transport by glucagon as well as by the ionophore can be blocked by the simultaneous addition of cycloheximide (0.1 mM) or actinomycin D (3.2 uM). In the absence of MIX, there is about a two-fold increase in the level of cAMP in response to glucagon. In the presence of MIX, glucagon causes more than 100-fold increase in the level of cAMP. The presence or absence of calcium does not affect the basal or glucagon-stimulated production of cAMP in these cultures. We have reported previously that, in monolayer cultures of rat hepatocytes, calcium repletion enhanced the glucagon stimulation of AIB transport while it markedly inhibited the production of cAMP in response to glucagon. It is suggested that calcium rather than cAMP has a direct effect on the amino acid transport system. (Author abstract) (24 Refs)

7. ESTABLISHMENT OF GONADOTROPIN-RESPONSIVE MURINE LEYDIG TUMOR CELL LINE.

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J Cell Biol; 94(1):70-76 1982

Several clonal Leydig tumor cell lines have been established by adapting the transplantable Leydig tumor, M548OP, to culture. One of these cell lines, MLTC-1, has been characterized with regard to the gonadotropin-responsive adenylate cyclase system. The binding of 125I-labeled human chorionic gonadotropin (hCG) was blocked by excess unlabeled hCG and lutropin (LH) but not by follitropin, thyrotropin, or insulin, indicating the presence of specific receptors for hCG and LH. Based on the specific binding of hCG to isolated MLTC-1 membranes, the calculated dissociation constant was 1.0 +-0.2 x 10(-10) M. The receptors appeared identical to those from normal murine Leydig cells when analyzed by SDS PAGE and sucrose density gradient centrifugation. The molecular wt and sedimentation coefficient were 95,000 daltons and 8.5 S, respectively. MLTC-1 cells responded to hCG by accumulating cyclic AMP and producing progesterone. Cyclic AMP accumulation was time- and dose-dependent with a maximal accumulation occurring at approx 0.2 nM hCG. At saturating levels of hCG, cAMP levels reached a max by 30 min and then declined very slowly. Adenylate cyclase activity in membranes prepared from MLTC-1 cells was stimulated by hCG, LH, NaF, cholera toxin, and guanyl-5'-ylimidodiphosphate. Additionally, choleragen was found to ADP-ribosylate a membrane protein of 54,000 daltons. This protein resembles the proposed guanine nucleotide regulatory component in both size and choleragen-dependent reactivity. These data suggest that MLTC-1 cells possess a gonadotropin-responsive adenylate cyclase system consisting of a specific hormone receptor, a regulatory component, and a catalytic subunit. (Author abstract) (40 Refs)

8. ALTERED GLYCOSYLATION OF CHORIOGONADOTROPINS FROM JEG-3 CELL CULTURE (MEETING ABSTRACT).

Kellen JA, Malkin DG, Chan AW, Malkin A
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Proc Am Assoc Cancer Res; 23:928 1982

Plant lectins are useful probes for studying protein glycosylation, and can be used to indicate chemical alterations in cell surface architecture and products from malignant cells. The JEG-3 model used in this study is derived from a human trophoblastic tumor and is known to actively secrete choriogonadotropins (CG) in cell culture. We studied binding of the secreted CG to Concanavalin A (Con A) and Ricinus conjugated Sepharose 4B columns, in comparison with the product of normal 3rd trimester placental cells and after a pulse of gonadoliberin (LHRF, 1 ug/ml), dbCAMP (lmM), Con A (100 ug/ml) and Wheat Germ lectin (100 ug/ml), respectively. CG was determined by radioimmunoassay (RIA) using an antibody to the beta subunit. Our results indicate that while the CG released by normal trophoblast cells into the culture medium is 90% Con A-bound, up to 40% of CG from JEG-3 is not bound to this lectin; however, 25% of this 'free' fraction binds to Ricinus and is therefore glycosylated, containing D-Gal moieties. Exposure of JEG-3 cultures to LHRF, Con A, and dbCAMP increased CG secretion, but did not alter the proportions of CG binding to these lectins. Wheat Germ agglutinin inhibited cell growth. We conclude that malignant cells of trophoblastic origin synthesize a substantial part of CG with an altered pattern of glycosylation. This pattern is characteristic and constant, it does not change with increase or decrease of CG synthesis in the cell culture nor with numerous passages. (1 Ref)

9. PROLACTIN STIMULATES THE GROWTH OF HUMAN PROSTATIC CARCINOMA CELL LINE DU-145 (MEETING ABSTRACT).

Webber MM, Wettlaufer JN
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In Vitro; 18(3,part2):323 1982

Cancer of the prostate is one of three leading causes of death in the adult male cancer patient yet little is known about its etiology. The long-term goals of this study are to examine the role of prolactin (P) in growth, maintenance, functions and behavior of prostatic epithelium and its possible growth enhancing effects on prostatic cancer. DU-145 cells were grown in RPMI-1640 medium containing 2% fetal bovine serum. Ovine prolactin was incoporated into the culture medium in dose levels varying from 10(-8) IU/ml to 1.0 IU/ml. Medium was changed every other day. Cells were counted nine days after plating. Results show that levels as low as 10(-8) IU/ml stimulated growth which increased with concentration, and 10(-1) IU/ml induced maximal growth showing a four-fold increase in cell number over control cultures. Prolactin shows a bell-shaped dose-response curve. These findings are of considerable significance in determining the possible tumor enhancing effects of P in light of the fact that P levels increase with age in the human male. Carcinoma of the prostate is often treated with estrogens, which increase P secretion. (no Refs)

10. GROWTH OF RAT MAMMARY TUMOR LINES IN CELL CULTURE (MEETING ABSTRACT).

Richards J, Osborn R
Cancer Research Laboratory, University of California, Berkeley, CA, 94720
Proc Am Assoc Cancer Res; 23:918 1982

Four different transplantable rat mammary tumor lines were cultured in a rat tail collagen gel matrix, on plastic, or in agar in an attempt to develop means of characterizing tumors with respect to their hormone responsiveness and metastatic potential. The tumor tissue was dissociated by collagenease (0.1%) and hyaluronidase (0.1%) treatment and the epithelial cells isolated on a Percoll equilibrium density gradient. The lines studied were R3230AC, a well differentiated hormone-responsive tumor that occasionally metastasizes; 13762NF, a hormone-responsive, highly metastatic tumor; 3M2N, a squamous cell carcinoma of low metastatic potential; and DMBA number 1, a papillary-cystic adenocarcinoma that rarely metastasizes. All tumors grew well in collagen gels; R3230AC, 3M2N and 13762NF grew on plastic and 13762NF also grew in soft agar. Growth respnses to various combinations of insulin, prolactin, hydrocortisone, estradiol, progesterone, dihydrotestosterone, cholera toxin and epidermal growth factor (EGF) were examined. Cholera toxin was the most stimulatory of the factors added but stimulated only R3230AC and 3M2N. With the exception of hydrocortisone, the hormones were not significantly growth stimulatory. EGF promoted growth of R3230AC and 13762NF and also affected colony morphology. Within the collagen gel matrix, the tumor cells produce colonies with various morphologies, depending on the tumor, serum concentration and factors present in the medium. This variation in colony morphology is not seen on plastic and may be of value in characterizing the heterogeneity within the tumors with respect to cells' growth requirements, metastatic potential and drug sensitivity. (no Refs)

11. BIOCHEMICAL EVENTS ASSOCIATED WITH MITOGENIC STIMULATION OF NB 2 NODE RAT LYMPHOMA CELLS BY PROLACTIN (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:903 1982

The growth of Nb 2 node rat lymphoma cell cultures (doubling time ca 20 hr) is critically dependent on the presence in the medium of lactogens, eg rat, bodine, ovine prolactin (PRL). Culture growth was found to cease about 18 hr after transferring cells to medium deficient in lactogens. By this time synthesis of both DNA and RNA (as measured by nucleoside incorporation) had fallen to very low levels and the activities of ornithine decarboxylase (ODC) and S-adenosyl methionine decarboxylase (SAMD), measured in cell extracts, were barely detectable. When ovine PRL (1-20 ng/ml) was added to these stationary cultures, the cell population did not change for ca 22 hr but then rapidly increased to almost double. DNA synthesis increased sharply ca 10 hr after PRL addition, showing a well-defined wave which preceded the increase in cell numbers. In contrast, there was an almost immediate, very marked increase in RNA synthesis. ODC and SAMD activities both rose sharply ca 4 hr after PRL addition and showed other well-defined changes as the cells proceeded towards division. These results and quantitative analysis of intracellular DNA by flow-cytometry show that, in lactogen-deficient medium, the lymphoma cells accumulated in the early G1 phase of the cell cycle, from which on stimulation by PRL they proceeded in a synchronized fashion through the cycle. (no Refs)

12. THE EFFECT OF CHEMICALLY DEFINED SERUM-FREE MEDIUM ON CELL LINES OF HUMAN RENAL CANCER: PROPAGATION. GROWTH REQUIREMENTS, AND TUMORIGENICITY (MEETING ABSTRACT).

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In Vitro; 18(3,part2):306 1982

Biochemical studies of human renal cell cancer (RCC) have been hampered by the lack of a chemically defined, serum-free medium (SFM). Herein we report the growth of two cell lines of human RCC on a form of SFM developed by Taub. Four cell lines of human RCC were studied: 786-0, 769-P, 1072-F, and Caki-1. Twelve-day growth curves were obtained for each line using: SFM, serum-containing medium (SCM), and a control medium. In addition, cells propagated on SFM were subcultured, plated on agar, and also inoculated into athymic mice. Finally, hormonal-exclusion studies were performed with hydrocortisone, prostaglandin E1, insulin, transferrin, and triiodothyronine. Only 786-0 and Caki-1 had similar growth rates on SFM and SCM. The plating efficiency on SFM was 30-50% less than on SCM. The hormonal-exclusion studies revealed transferrin, hydrocortisone, and insulin essential factors for 786-0 and insulin to be the only necessary factor for Caki-1. Following growth on SFM, both cell lines continued to produce colonies in agar and Caki-1 also produced tumors in athymic mice. To date, 786-0 and Caki-1 have been maintained in continuous culture on SFM for more than 7 months and have undergone 10 and 13 passages, respectively. (no Refs)

13. TOXICITY OF MULLERIAN INHIBITING SUBSTANCE TO CELLS DERIVED FROM A HUMAN ENDOMETRIAL TUMOR (MEETING ABSTRACT).

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In Vitro; 18(3,part2):323 1982

A cell line (HEC-1A) derived from a human endometrial tumor is responsive to the presence of Mullerian Inhibiting Substance (MIS) when grown in McCoy's medium in the absence of serum but with the addition of insulin (5 ug/ml), transferrin (5 ug/ml), hydrocortisone (50 nM), EGF (epidermal growth factor) (10 ng/ml) and FGF (fibroblast growth factor) (50 ng/ml). These cells exhibit a 40% reduction in the incorporation of 3H-TDN within 12 h following the addition of MIS to the cultures when compared to similar cultures without MIS. Cells maintained in McCoy's medium with 15% fetal bovine serum show no response to MIS. Other experiments indicate that serum does not inhibit the action of MIS. MIS, isolated for these experiments from neonatal calf Sertoli cells, is a testicular glycoprotein which causes the involution of the Mullerian duct during development of the male fetus. Because the Mullerian duct is the anlage of the uterus and uterine tubes in mammals, it is postulated that cells derived from tumors of Mullerian duct origin must reacquire a sensitivity to the action of MIS by presence of fetal antigens on their cell surface. Additionally, serum must inhibit either the formation or expression of these antigens. (no Refs)

CLINICAL, DIAGNOSTIC AND PROGNOSTIC STUDIES

14. CIRCULATING IMMUNE COMPLEX LEVELS IN PATIENTS WITH GESTATIONAL TROPHOBLASTIC NEOPLASIA.

Rayner AA, Berkowitz R, Steele G, Schur PH, Rodrick ML, Goldstein DP, Harte PJ, Wilson RE, Zamcheck N, Munroe AE
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JNCI; 69(1):23-26 1982

The clinical course, human chorionic gonadotropin (HCG) levels, and serial circulating immune complex (CIC) levels in 21 patients with gestational trophoblastic neoplasia (GTN) were correlated for the evaluation of the relationship between CIC levels and trophoblastic tumor burden. CIC levels were normal in 18 of 21 patients at the time of presentation, and 2 of the 3 patients who presented with elevated CIC levels had significant comorbid disease (toxemia and hepatitis). Nine patients were followed into gonadotropin remission, and all nine developed an increase in CIC levels at the time of remission. It was concluded that CIC, at least as measured by two antigen-nonspecific techniques, is generally not elevated at initial presentation in the patient with GTN; this lack of an elevation is probably due to marked tumor antigen excess. Thus the in vivo importance of CIC as a 'blocker' of host antitumor response at this stage is doubtful. After effective treatment as HCG levels return to normal, the demonstrated elevation in serial levels of CIC may reflect a return of adequate host immune response at a time of minimal tumor burden. (Author abstract) (16 Refs)

15. THE CLINICOPATHOLOGIC PROFILE OF THE PARTIAL HYDATIDIFORM MOLE.

Szulman AE, Surti U
Dept. Pathology, Magee-Womens Hosp., Pittsburgh, PA, 15213
Obstet Gynecol; 59(5):597-602 1982

Having delineated the complete and the partial hydatidiform moles as 2 separate entities on the basis of morphology and cytogenetics, the authors studied 201 molar pregnancies at the Magee-Womens Hospital in an attempt to characterize the clinicopathologic profile of the partial mole syndrome. This was done mainly by comparison and contrast with the established and more familiar syndrome of the classic complete mole. The partial mole syndrome displays most of the pathologic and clinical features of the classic mole and seems to represent a milder, dilute version of the latter. This applies to placental morphology, to the fate of the embryo/fetus, and to human chorionic gonadotropin (hCG) levels as well as to the incidence and severity of clinically persistent trophoblastic disease. Preeclampsia can be equally severe in both syndromes, but tends to occur later in patients with partial mole. No metastatic disease was encountered in association with partial moles and no case of overt choriocarcinoma has yet been described. The occurrence of trophoblastic disease (as determined by postoperative hCG titers) following partial moles requires further inquiry, including study of the pathology of the underlying lesion(s), which remain virtually unexplored. (Author abstract) (22 Refs)

16. SERUM SP1 AND HCGBETA-SUBUNIT (HCGBETA) LEVELS IN CHORIOCARCINOMA, INVASIVE MOLE, AND HYDATIDIFORM MOLE - CLINICAL SIGNIFICANCE OF SP1/HCGBETA RATIO.

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Gynecol Oncol; 13(3):393-398 1982

Serum Sp1 (pregnancy-specific beta1 glycoprotein) levels in patients with choriocarcinoma, invasive mole, and hydatidiform mole were radioimmunoassayed and compared with simultaneously measured serum hCGbeta-subunit (hCGbeta) levels in order to evaluate the clinical significance of SP1 determination. Serum SP1 levels at the time of admission ranged from 6.4 to 1,660 ng/ml in choriocarcinoma patients, 16.3 to 540 ng/ml in invasive mole, and 720 to 58,000 ng/ml in hydatidiform mole. Sp1/hCGbeta ratios were under 1.0 in choriocarcinoma (0.3 +-0.2, mean +- SD), over 1.0 in hydatidiform mole (10.9 +-8.3), and intermediate in invasive mole (1.5 +-0.3). In normal pregnancy, the ratio increases as pregnancy progresses, that is, from 15.25 in 7-wk gestation to 14,090.90 in 40-wk gestation. The mean SP1/hCGbeta ratio differs significantly among choriocarcinoma, invasive mole, and hydatidiform mole. SP1/hCGbeta ratio is likely to represent the degree of differentiation of trophoblastic cells. The SP1/hCGbeta ratio may be useful in differentiating between choriocarcinoma and invasive mole. (Author abstract) (4 Refs)

17. GONADOTROPHIN-PRODUCING SEMINOMA: A DISTINCT CATEGORY OF GERM CELL NEOPLASM.

Morgan DA, Caillaud JM, Bellet D, Eschwege F

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Clin Radiol; 33(2):149-153 1982

Gonadotrophin-producing seminomas can be identified in two ways: detection of human chorionic gonadotrophin (HCG) in the serum or urine, or histological identification of syncytiotrophoblastic giant cells, which can be shown to contain HCB by means of indirect immunoperoxidase techniques. A review of the histories of 14 patients with such tumors shows that they are associated with a worse prognosis than that of 'typical' seminomas, and tend to present with a more advanced stage of disease. These tumors are thus distinct, clinically and biologically, from typical seminomas, and their treatment needs to be planned accordingly. (Author abstract) (15 Refs)

18. THE ESTROGENIC RECEPTOR IN DESMOID TUMORS. PRELIMINARY REPORT.

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Arch Invest Med (Mex); 13(2):105-108 1982

Estrogenic hormonal receptor (ER) was studied in six patients with a histologic diagnosis of desmoid tumor. Pertinent clinical characteristics and ER levels are summarized. In five out of six patients measurable amounts of ER 4-64 femtomole(fmol)/mg protein were found and in three of the patients values were considered to be positive (greater than 10 fmol/mg protein). The levels of gonadotrophins and estradiol 17 B were normal in all patients; prolactin was discretely elevated in two patients; and in isolated patients in which growth hormone and testosterone were measured, they proved to be normal. (19 Refs)

19. HYPERGONADOTROPIC HYPOGONADISM, SHBG DEFICIENCY AND HYPERPROLACTINAEMIA: A TRANSIENT PHENOMENON DURING INDUCTION CHEMOTHERAPY IN LEUKEMIC CHILDREN.

Beck W, Schwarz S, Heidemann PH, Jentsch E, Stubbe P, Konig A
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Eur J Pediatr; 138(3):216-220 1982

Hypothalamo-pituitary-gonadal function was evaluated in five pubertal boys (16-19 yr old) and four prepubertal girls with acute lymphoblastic leukemia before and during (day 10, 21 and 28) and 23 days after the induction phase of treatment with vincristine (VCR), daunorubicin (DAU), L-asparaginase (ASP), and prednisone (PR). After 3 wk of therapy, plasma testosterone and estradiol levels decreased while both boys and girls showed decreased binding capacity of sex-hormone-binding globulin. Testicular volume in boys also was decreased. At the same time basal luteinizing hormone (LH), follicle stimulating hormone, and prolactin values doubled with a normal gonadotropin response to LH releasing hormone. The prolactin response to thyrotropin-releasing hormone increased at the end of the induction phase, when treatment with VCR, DAU, and ASP were discontinued, while PR was continued for 7 days. All hormonal values, and testicular volume in boys, became normal within a period of 3 wk after induction therapy, despite continued therapy with other antileukemic agents and radiotherapy. The mechanisms involved in these hormonal and gonadal changes are discussed. (35 Refs)

20. MOLECULAR HETEROGENEITY OF HCG AND HCG-SUBUNITS IN MALIGNANT TESTICULAR TUMORS.

Mann K, Gilch R, Haidl P, Hellmann T, Karl HJ
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Verh Dtsch Ges Inn Med; (87):620-622 1981

Levels of serum human chorionic gonadotropin (HCG) and HCG subunits were measured in patients with nonseminomatous malignant testicular tumors prior to surgery, in healthy controls, and in patients with nontumorous diseases. Sera from patients with testicular tumors contained HCG and alpha- and beta-chains of HCG. The level of beta-chains was far below that of HCG and did not affect radioimmunologic determination of HCG. Variant forms of HCG were found in sera from the tumor patients; these variants were not found in sera from pregnant women. (5 Refs) (In GER)

21. TUMOR MARKERS IN TESTICULAR NEOPLASMS (MEETING ABSTRACT).

Schmoll HJ, Von zur Muhlen A
Dep. Innere Medizin und Dermatologie, Med. Hochschule Hannover, Hannover, W. Germany
Onkologie; 4(5):263 1981

In 172 patients with malignant tumors of the testis (39 patients stage I, 42 patients stage II a/b, 91 patients stage IIc-IIIb) the following serum values were determined consecutively over a 6-36 mo period: beta-human chorionic gonadotropin (beta-HCG), alpha-fetoprotein, lactate dehydrogenase (LDH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, estriol (E1) estradiol (E2), total estrogens, triiodothyronine (T3), thyroxine (T4), rT3. During the course of the disease in patients in stages IIa-IIIb there was an increase in alpha-fetoprotein in 62% of the patients, in beta-HCG in 54%, in LDH in 34%, LH in 64%, FSH in 25%, E1 in 64%, E2 in 67%, and total estrogens in 39%. Whereas the elevation of FSH, E1 and E2 during the period without clinical disease was only followed by progression or recurrence in 40% of the patients, recurrence or progression of their disease occurred on av 3 mo after the increase in serum levels in 70% of the patients with a rise in total estrogens to twice normal values and in 96% of those with triple the normal levels. T3, T4, and rT3 fell within the normal range. The results suggest that estrogens can be produced by a non-seminomatous tumor of the testis and that their measurement can be of value both prognostically as well as for monitoring therapy and the course of the disease. (no Refs) (In GER)

22. SERIAL ASSESSMENT OF FOLLICLE-STIMULATING HORMONE (FSH), LUTEINIZING HORMONE (LH), TESTOSTERONE (T), AND ESTRADIOL (E) DURING CHEMOTHERAPY FOR ADVANCED TESTIS CANCER (MEETING ABSTRACT).

Trump DL
University of Wisconsin, Madison, WI, 53792
Proc Am Soc Clin Oncol; 1:C-474 1982

FSH, LH, T, and E were measured in plasma samples from 15 patients during administration of either vinblastine (V), bleomycin (B), cisplatin (P), cyclophosphamide, actinomycin D [VAB III] (8 patients), or VBP (7 patients). All patients had a normal plasma concentration of the beta subunit of human chronic gonadotropin (betaHCG). Prior to therapy FSH and T were normal, while LH and E were slightly increased. After induction chemotherapy, FSH and LH increased markedly: mean FSH -1169 ng/ml, normal -98-276 ng/ml; mean LH -132 ng/ml, normal -36-64 ng/ml. T and E were unchanged. During the maintenance phase of VAB III, FSH and LH remained elevated while T and E were unchanged. Three to six months after cessation of chemotherapy FSH remained increased; by 12-18 months FSH was returning toward normal. LH remained elevated at both the 3-6 month and 12-18 period. Mean T was normal, and mean E remained slightly increased during post-therapy followup. Fourteen of 15 patients achieved a complete remission, and 13 remain free of disease at 6-24 months. During chemotherapy three patients developed painful gynecomastia with undetectable betaHCG, high FSH and LH, normal T, and high E. These data indicate that cisplatin-based chemotherapy damages the germinal epithelium and testicular Leydig cells. Plasma T concentrations are generally maintained but require very high FSH and LH levels. E may be increased by testicular synthesis or enhanced peripheral conversion from androgenic precursors. (no Refs)

23. PREGNANCY-SPECIFIC BETA1 GLYCOPROTEIN IN THE SERUM IN NON-SEMINOMATOUS TESTICULAR TUMORS (MEETING ABSTRACT).

Bauer HW, Sturm W, Mann K, Lamerz R
Urologische Universitatsklinik, Munchen 70, W. Germany
6. Symposium fur Experimentelle Urologie, April 15-17, 1982, Bonn, W. Germany. German Association for Urology 155 pp., 1982.

The extent to which pregnancy-specific beta 1 glycoprotein (SP1) is found in the serum in non-seminomatous tumors of the testis will be investigated. SP1 is a trophoblast antigen the same as beta-human chorionic gonadotropin (betahCG). Analysis of 205 sera from 75 patients was performed by means of enzyme immunoassay for SP1 and radioimmunoassay for betahCG. Approx one-third of the patients with non-seminomatous tumors of the testis had elevated SP1 concentrations in their sera. We found no patients with normal betahCG levels who had elevated beta 1 glycoprotein concentrations. A methodologic comparison between a radioimmunoassay for SP1 used earlier and the present enzyme immunoassay revealed the enzyme immunoassay to have greater significance because of its higher sensitivity. Based on the present series we concluded that the determination of pregnancy-specific beta 1 glycoprotein furnishes no additional information clarifying non-seminomatous tumors of the testis. (no Refs) (In GER)

24. ENDOCRINOLOGY AND MARKERS IN TESTICULAR TUMORS (MEETING ABSTRACT).

Scheiber K, Bartsch G
Univ.-Klinik Innsbruck, Innsbruck, Austria
Onkologie; 4(5):263 1981

Endocrine changes in tumors of the testis can be produced by 3 mechanisms: direct synthesis of androgens and estrogens by the tumor, synthesis of gonadotropins such as human chorionic gonadotropins (HCG) or somatotropic chorionic hormone (SCH) which in turn stimulate production of androgens or estrogens, and changes in peripheral androgen balance. Various parameters of the pituitary-gonadal axis were measured in patients with seminomas and malignant teratomas before and during treatment: LH (luteinizing hormone), FSH (follicle stimulating hormone), prolactin, testosterone, 17beta-estradiol and these values were contrasted with beta-HCG and alpha-fetoprotein. (no Refs) (In GER)

25. THE PARADOXICAL ROLE OF BROMOCRYPTINE IN THE MANAGEMENT OF ADVANCED CANCER OF THE PROSTATE (MEETING ABSTRACT).

Bush IM, Lanners J, Cohen E, Ablin RD, John T, Sadoughi N, Guinan P
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Twenty of twenty-seven consecutive patients with D2 cancer of the prostate and painful osseous metastasis in spite of estrogen therapy +/- orchiectomy +/- chemotherapy +/- local radiation therapy, found to have elevated levels of serum prolactin, 19-86 ng/ml (normal our laboratory, 5-18 ng/ml), were given, in addition to ongoing therapy, bromocryptine 2.5 to 15 mg/day for up to 25 months. Survival was longer in the 13 patients (5 to 25 mos; mean, 11.4 mos) when elevated prolactin levels (mean, 30 ng/ml) fell on bromocryptine therapy below 16 mg (mean 8.2 ng/ml) than in the 7 patients whose initial elevated prolactin levels (mean, 29 ng/ml) were not reduced (mean, 27 ng/ml) in spite of bromocryptine therapy (2 to 13 mos, mean, 6.3 mos). Elevation of serum prolactin levels in patients with advanced prostatic cancer usually occurs after an extended period of estrogen therapy (6-55 mos; mean, 22 mos). No bone lesion was considered improved on x-ray, however, serial bones scans may have improved in two patients. Bone pain was relieved in 9 of the 13 responders to a variable extent. However, in 4 of these patients who inadvertantly stopped medication, bone pain returned within three weeks. A large hilar mass that occurred in spite of cis-platinum therapy disappeared and has not reoccurred to date. (no Refs)

26. PROLACTIN AND ENDOMETRIAL ADENOCARCINOMA.

Volpe A, Di Renzo GC
Istituto di Clinica Ostetrica e Ginecologica, Universita di Modena, via del Pozzo 71, Modena, Italy
Gynecologie; 33(1):77-83 1982

The plasma levels of prolactin (PR) were determined in 40 patients (av age 59.5 yr) with endometrial adenocarcinomas and in 40 matched healthy controls. The PR levels were found to be higher in the patients than in the controls, but the pituitary the patients. The in vitro production of PR in cancer tissue cultures was found to be higher than in normal endometrial tissue cultures. In vitro PR secretion by endometrial adenocarcinoma cells was found to be significantly higher than secretion by normal adenocarcinoma is assumed to be of endometrial origin. (17 Refs) (In FRE)

27. USEFULNESS OF CLINICAL CHEMISTRY MEASUREMENTS IN CLASSIFYING PATIENTS WITH BREAST CANCER.

Statland BE, Winkel P
Dept. Lab. Medicine, Univ. Hosp., Boston Univ. Medical Center, Boston, MA
CRC Crit Rev Clin Lab Sci; 16(4):255-290 1982

Laboratory measurements can be used to detect, classify, and monitor patients with breast cancer. This review covers in detail the clinical usefulness of carcino embryonic antigen, tissue polypeptide antigen, various glycoproteins, pregnancy-associated proteins, casein, lactalbumin, beta-2-microglobulin, ferritin, immunoglobulins, acute phase proteins, placental-like alkaline phosphatase, liver-associated enzymes, glycosyltransferases, human chorionic gonadotropin, calcitonin, polyamines, and collagen breakdown products, in relationship to their diagnostic utility in patients suspected of having or known to have breast cancer. In addition, these authors assess the merits of various multivariate techniques using a number of clinical chemistry quantities in the same regard. Finally, the relative contribution of biochemical tests vs the information values gained from 'surgical pathology' data (number of positive nodes, number of negative nodes, and degree of anaplasia) is discussed. (Author abstract) (165 Refs)

28. BREAST TUMORS IN PATIENTS WITH HYPERPROLACTINEMIA.

Brown RW, Meehan C, Martin FI, Bhathal PS
(c/o Martin) Post Office, Royal Melbourne Hosp., Victoria, 3050, Australia
Cancer; 50(1):125-129 1982

The histology of breast lumps in five patients with hyperprolactinemia showed benign mammary dysplasia with vacuolation of acinar and duct lining cells. In two cases, foci of lobular development resembling lactating breast tissue were also noted. In the past, focal secretory change has been considered to be idiopathic, but these cases indicate a possible association with hyperprolactinemia. Among other causes hyperprolactinemia may be a manifestation of occult pituitary adenoma. Therefore it is suggested that patients with benign breast nodules showing focal secretory change should be screened for clinical and laboratory evidence of hyperprolactinemia. Although it is accepted that in mice and rats prolactin plays an important role in chemically induced mammary tumorigenesis, a consensus has not been reached with regard to its role in man. (Author abstract) (17 Refs)

29. ASSESSMENT OF HORMONE SENSITIVITY OF HUMAN MAMMARY TUMORS BY DIFFUSION CHAMBER CULTURE.

Lahiri T, Chowdhury TJ
Dept. Endocrinology, Chittaranjan Natl. Cancer Res. Centre, Calcutta 700 026, India
Tumor Res (Sapporo); 16:1-6 1981

The use of diffusion chamber culture techniques in evaluating the hormone responsiveness of human tumors in altered endocrine conditions of the host including (1) induction of hyperprolactinemia by pituitary stalk section, (2) removal of primary source of estrogen by bilateral oophorectomy, or (3) both procedures, is reported. While human breast adenocarcinoma cells grew in diffusion chambers for up to 21 days, experiments following endocrine ablations were restricted to 7 days where cells were uniform in size and shape with prominent nucleoli. Elevation of prolactin by pituitary stalk section induced growth stimulation in 83.3% tumors in the diffusion chamber culture compared to 11.1% in intact controls. A mixed response was observed when prolactin elevation was combined with withdrawal of estrogen; 36.3% of tumors showing growth stimulation and 45.4% displaying normal growth patterns. Oophorectomy alone caused inhibition of 45.4% of tumors and activation in only 9%. Mean cell count of human adenocarcinoma grown in diffusion chamber culture increased from 7.4 x 10(7) in the intact to 18.3 x 10(7) in the stalk sectioned group. Oophorectomy induced a drop in cell count to 3.1 x 10(7) in chamber culture. Mitotic index increased in the stalk sectioned group and decreased in the oophorectomized group. Succinic dehydrogenase (SD) activity was observed in 35.8% of cells from tumors of stalk sectioned group, compared to 13.2% in intact controls. Following oophorectomy the mean percentage of cells showing high and moderate activity fell, with 55.8% of cells displaying low SD activity. (20 Refs)

30. ARGYROPHILIC BREAST CARCINOMAS. EVIDENCE OF LACTATIONAL DIFFERENTIATION.

Clayton F, Sibley RK, Ordonez NG, Hanssen G
Dept. Pathology, LDS Hospital, 325 8th Avenue, Salt Lake City, UT, 84243
Am J Surg Pathol; 6(4):323-333 1982

Twenty unselected breast carcinomas were examined for the presence of argyrophilia, dense-core secretory granules, and lactalbumin to determine whether the secretory product of argyrophilic breast carcinomas might represent milk protein rather than neuroendocrine polypeptide hormones. None of the patients developed carcinoid syndrome during a follow-up period averaging 1 yr. All four strongly argyrophilic carcinomas contained estrogen receptors, although in two, levels were borderline. The histologic pattern, the degree of silver impregnation, and the fine structural and immunoperoxidase findings are listed. The tumors were segregated into three groups: positive lactalbumin immunoperoxidase staining with either argyrophilia, ultrastructural dense-core secretory granules or both; no lactalbumin staining but weak to moderate argyrophilia or dense-core granules by electron microscopy; and negative lactalbumin, argyrophilia, and dense-core secretory granules. Ten of the cases showed varying degrees of argyrophilia but ultrastructural evidence of dense-core neurosecretory-like granules were found in only eight of the tumors. Of the 20 cases studied, 50% demonstrated varying degrees of argyrophilia and 65% contained dense-core, secretory granules. While immunoperoxidase staining for insulin, glucagon, ACTH, gastrin, calcitonin, somatostatin, prolactin, and pancreatic polypeptide were all negative in the five strongly argyrophilic cases, specific intracytoplasmic round granular staining for lactalbumin was found in all five tumors. The common occurrence of argyrophilia and dense-core secretory granules in breast carcinoma and lactating breast was demonstrated. (25 Refs)

31. HYPERPROLACTINEMIA AND BROMOCRYPTINE IN METASTATIC BREAST CANCER (MEETING ABSTRACT).

Nagel GA, Holtkamp W, Wander HE, Blossey CH
Department of Hematology/Oncology, Medical University Clinics, D-3400 Goettingen, W. Germany
Proc Am Assoc Cancer Res; 23:548 1982

From the literature there is evidence that hyperprolactinemia (HPRL) is an indicator of poor prognosis in metastatic breast cancer. In order to further substantiate such preliminary communications serial plasma prolactin (PRL) determinations were done in 220 patients (pts) with metastatic breast cancer (bc) and correlated to chemotherapy (ct) results. PRL was measured by radioimmunoassay (range of normal controls 50-500 iu/l). HPRL was defined as PRL greater than 1000 iu/l. HPRL occurred in 25 % of the pts with an equal distribution in pre- and postmenopausal pts but a predominance in mother/daughter type familial bc. In pts with HPRL bc appeared to be a very aggressive disease with a rapid disease development, multiple organ and early brain involvement. The overall remission rates with first line CMF (cyclophosphamide, methotrexate, 5-fluorouracil) or VAC (vincristine, actinomycin D, cyclophosphamide) ct were 63% for all pts and 27.5% for HPRL pts. Median remission rate, duration and survival was shorter for HPRL pts. In 22 pts with HPRL refractory to CMF or VAC this ct was continued with the addition of Bromocryptine 10 mg/daily. This combined therapy resulted in normalization of PRL in 22/22 and remissions in 12/22 pts. In conclusion, pts with HPRL bc have a poor prognosis. There is an association between rapid tumor progression, HPRL and resistance to ct. Normalization of PRL by Bromocryptine increases ct remission rates. (no Refs)

32. MEDICAL ADRENALECTOMY WITH AMINOGLUTETHIMIDE (AG) AND TAMOXIFEN (T) FOR METASTATIC BREAST CANCER (MBC) - EFFECT ON RESPONSE (R) AND PITUITARY HORMONES (MEETING ABSTRACT).

Ragaz J, Leahy M, Ibrahim E, Spinelii J, Willan AR
CCABC, Vancouver, British Columbia, Canada
Proc Am Assoc Cancer Res; 23:571 1982

Two hundred forty-one post-menopausal patients (pts) with MBC were treated with AG with or without T. The following observations were made: in all 3 groups, the duration of past-hormonal therapy (PHT) has not affected the R - pts with 0, 1-12, and 13+ mo of PHT had a R of 34.3%, 38.9%, and 31.8% respectively On the other hand, the duration of past-chemotherapy (PCh) adversely influenced the R. Patients with 0, 1-12, 13+ mo of PCh had a R of 46.0%, 21.5% and 17.4% respectively. For patients with AG: 1) 13 pts with high prolactin (Prol) had 0% R, whereas 58 pts with low Prol had R of 37.9% (p equals 0.01); 2) On chronic therapy, we observed an initial increase and subsequent decrease of follicle stimulating hormone (FSH), compared to the pre-treatment levels. R in pts with high FSH and low Prol was higher (52%) than R in pts with low FSH low Prol (21.4%) (p equals less than 0.1). 3) In 6 pts failing therapy, progressive decrease of FSH down to the premenopausal values and way below the post-menopausal range was documented. As well, in some of these pts, increasing, or above the normal, serum Prol levels were observed at the same time. 4) Thyrotropin values gradually increased (p equals 0.009) and dehydroepiandrosterone (DHA-S) levels remained suppressed on chronic therapy. No significant changes were observed for LH and Cortisol. (no Refs)

33. BROMOCRIPTINE IN MANAGEMENT OF LARGE PITUITARY TUMOURS.

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Br Med J; 284(6333):1908-1911 1982

Bromocriptine has an accepted place in the management of small pituitary tumors that secrete either prolactin or growth hormone. The treatment of large tumors with extrasellar extensions is more difficult, however: though surgery is the standard treatment, it is often unsuccessful in returning excessive hormone secretion to normal and may cause hypopituitarism. A prospective trial was undertaken to assess the frequency with which changes in pituitary function and size of large tumors occurs. Nineteen patients were studied before and during treatment with bromocriptine (7.5 to 60 mg/day) for 3 to 22 mo, using contrast radiology and a detailed assessment of pituitary function. Eighteen patients had hyperprolactinemia and 2 of these also had raised concentrations of growth hormone; 1 patient had an apparently non-functioning tumor. In 12 patients (63%) tumor size decreased with bromocriptine and no tumor enlarged. Nine patients had visual-field defects, which improved in seven, becoming normal in five. Pituitary function improved in nine patients (47%) becoming entirely normal in three. Bromocriptine should be the treatment of choice in patients with large pituitary tumors with extrasellar extensions, provided close supervision is maintained. (Author abstract) (35 Refs)

34. TWENTY-FOUR HOUR SECRETION IN PATIENTS WITH PRL OR GH SECRETING PITUITARY TUMOURS.

Giusti M, Bagnasco M, Mazzocchi G, Mignone D, Contessini M, Ciprandi G, Giordano G

Cattedra di Endocrinologia, Universita di Genoa, Viale Benedetto XV 6, 6132 Genova, Italy

IRCS Med Sci [Cancer]; 9(9):827-828 1981

Thyroid-stimulating hormone (TSH) circadian rhythm was studied in 23 patients (4 males, 19 females, 18-52 yr old, av 36 yr) with prolactinomas or acromegaly. A rhythmic TSH secretory pattern was observed in all control subjects. An alteration of TSH rhythmic secretion occurred in patients with circumscribed pituitary adenomas and an absence of TSH circadian rhythm and a reduction in the secretory amplitude of TSH was seen in acromegaly patients. Normal TSH rhythm did not reappear in prolactinoma or acromegaly patients following transsphenoidal adenomectomy. (15 Refs)

35. THE ACROMEGALY SYNDROME. RELATION BETWEEN CLINICAL FEATURES, GROWTH HORMONE VALUES AND RADIOLOGICAL CHARACTERISTICS OF THE PITUITARY TUMOURS.

Jadresic A, Banks LM, Child DF, Diamant L, Doyle FH, Fraser TR, Joplin GF

Endocrine Unit, Hammersmith Hosp., London W12 0HS, England

Q J Med; 51(202):189-204 1982

One hundred and fifty-five acromegalies, 76 males (mean age 44 +-1.3 yr) and 79 females (45 +-1.4 yr) were studied. The frequency of clinical features were: acral enlargement 100%, hyperhidrosis 65%, headache 55%, paraesthesiae 49%, cardiac problems 34%, hypertension 32%, diabetes mellitus (clinical and chemical) 27%, and visual field defects 6%. Signs and symptoms, and particularly headache, did not show any relation with the size or shape of pituitary tumors, nor with growth hormone (GH) values, age, sex or weight. Mean of GH values at 60, 90 and 120 min during a GTT averaged 135 mIU/l, range 8-1,833. Diabetes mellitus was more frequent and severe in patients with higher GH values, occurring in 32% of patients with mean GH values greater than or equal to 50 mIU/l and only in 16% of the rest (p less than 0.05). GH values correlated positively with size of tumors. Forty-nine percent of patients presented with entirely intrasellar tumors, 27% with suprasellar extensions and 23% with partially empty sellae. The mean GH (238 mIU/l) of patients with suprasellar extensions was significantly higher (p less than 0.004) than those of the others. Younger acromegalies showed a tendency to larger tumors. Early treatment of acromegaly, particularly in young patients and those presenting with high GH values, is recommended. (Author abstract) (61 Refs)

36. CLEAR CELL ADENOCARCINOMA OF THE VAGINA AND CERVIX IN BLACK FEMALES.

Johnston GA, Anderson D, Herbst AL, Hubby MM

Dept. Obstetrics and Gynecology, Ohio State Univ., 410 West 10th Ave., Columbus, OH, 43210

J Natl Med Assoc; 74(7):639-643 1982

Twenty-eight black females with clear cell adenocarcinoma of the vagina and cervix have been accessioned in the Registry for Research on Hormonal Transplacental Carcinogenesis. Most were born in the southern United States and histories of prenatal exposure to diethylstilbestrol were less frequent than with white patients. The characteristics of these cases were similar to those among whites in stage, variety of cell type, and patient survival. (Author abstract) (8 Refs)

37. GONADAL FUNCTION AFTER COMBINATION CHEMOTHERAPY FOR HODGKIN'S DISEASE IN CHILDHOOD.

Whitehead E, Shalet SM, Morris Jones PH, Beardwell CG, Deakin DP

(c/o Shalet), Christie Hosp. and Holt Radium Inst., Wilmslow Road, Manchester M20 9BX, England

Arch Dis Child; 57(4):287-291 1982

The effect of quadruple chemotherapy (mustine, vincristine, procarbazine and prednisolone) on gonadal function was investigated in 15 males and 2 females treated for Hodgkin's disease during childhood. The two females have regular menstrual cycles with evidence of ovulation in one. Twelve of the males have shown normal progression of pubertal development since completing their treatment. Nine out of 10 late pubertal or adult subjects had small testes but only one developed gynecomastia. All four prepubertal subjects had normal basal and peak gonadotrophin responses to luteinizing hormone-releasing hormone. Nine of the 12 subjects studied during puberty or adulthood had either an increased basal serum follicle-stimulating hormone (FSH) level or an exaggerated FSH response to luteinizing hormone-releasing hormone. Each of the six males who provided semen for analysis was azoospermic after an interval of between 2.4 and 8 (mean 5.3) yr after completion of treatment. We conclude that severe testicular damage is common after treatment with mustine, vincristine, procarbazine, and prednisolone in childhood. The germinal epithelium is particularly vulnerable and the resultant azoospermia is likely to be irreversible. The Leydig cells are less susceptible to cytotoxic-induced damage. Pubertal development is normal and there is no indication for androgen replacement therapy. (Author abstract) (20 Refs)

38. MEDULLARY CARCINOMA OF THE THYROID: RADIOGRAPHIC FEATURES OF A UNIQUE TUMOR.

McCook TA, Putman CE, Dale JK, Wells SA
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AJR; 139(1):149-155 1982

Medullary thyroid carcinoma occurs both sporadically and in families. When familial, it may be a component of the multiple endocrine neoplasia Type II syndromes characterized by medullary carcinoma of the thyroid (100% of patients), parathyroid hyperplasia (60% of patients), and pheochromocytoma (40% of patients). This unique neoplasm, whether sporadic or familial, is always associated with a biochemical marker, calcitonin, which defines the presence or absence of disease. Some patients exhibit radiographic features that may suggest the diagnosis and provide evidence of the extent of disease. Calcification in the primary tumor or cervical lymph nodes; mediastinal and hilar lymphadenopathy, sometimes calcified; fibronodular interstitial pulmonary disease, dense pulmonary nodules; lytic, blastic, or mixed bone lesions; and calcified liver metastases are evidence of the tumor. Associated pheochromocytomas are best sought initially by CT, but angiography may be required. Intestinal hypermotility is common. Despite functional hyperparathyroidism, associated radiographic abnormalities in the skeleton are seldom found. (Author abstract) (27 Refs)

39. THYROID TUMORS.

Tubiana M
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Rev Prat; 32(29):1925-1926,1929-1931 1982

Surgery is the treatment of choice for thyroid cancer. Thyroid cancer evolves very slowly which explains why certain metastases may only be revealed 20-25 yr after the treatment of the primary tumor. Treatment should be geared to the seriousness of the disease with the two most important prognostic factors being patient age and tumor histology. Unlike many other cancers, recurrences and metastases are compatible with long survival rates. It is suggested that thyroid hormones be given to patients with previously irradiated glands in order to inhibit production of thyroid stimulating hormone (TSH) because of the role of TSH in cancer initiation and growth. (14 Refs) (In FRE)

40. MEDULLARY CANCER OF THE THYROID. CLINICAL FORMS. DIAGNOSTIC AND THERAPEUTIC APPROACHES.

Rougier P, Travagli J, Schlumberger M, Caillou B, Lacour J, Gardet P, Parmentier C
Institut Gustave-Roussy, 39-53, rue Camille-Desmoulins, 94805 Villejuif, France
Rev Prat; 32(29):1997-2003 1982

Medullary thyroid (MTC) is a rare tumor of the thyroid which does not take up Iodine and is not influenced by thyroid stimulating hormone. Initial symptoms may include cervical nodules or functional signs such as diarrhea and flush. Diagnosis and surveillance of MTC is based on thyrocalcitonin and carcinoembryonic antigen. Treatment of choice is surgical excision. In cases where familial form of MTC is prevalent, relatives of patients should be screened for the disease. Post-treatment prognosis is good. (19 Refs) (In FRE)

41. CLINICAL STUDY ON INCREASED SERUM THYROXINE-BINDING GLOBULIN IN CANCEROUS STATE.

Kajita Y, Ishida M, Hachiya T, Miyazaki T, Yoshimura M, Ijichi H, Ochi Y
Dept. Internal Medicine, Nantan General Hosp. Yagi, Kyoto 629-01, Japan
Endocrinol Jpn; 28(6):785-791 1981

Serum levels of thyroxine-binding globulin (TBG) and thyroxine-binding prealbumin (TBPA) were determined in 169 patients with various cancers. Eleven patients with high TBG levels were studied for thyroid function and clinical courses were followed. Elevated TBG levels were measured in 6/80 patients with gastric cancer, 3/29 with colon cancer, 1/20 with lung cancer, 2/9 with primary liver cancer, 1/7 with breast cancer, 1/3 with uterine cancer, and 2/14 with other cancers. Of the 11 patients with high TBG level (greater than 35 ug/ml), 2 had been treated with estrogen and 1 had serum hepatitis after gastrectomy. Serum TBPA levels were decreased in 7/11 patients. Thyroxine (T4) was slightly increased or in the upper range in 9/11 patients. Clinical courses of patients without estrogen therapy and without liver dysfunction were reviewed. Serum TBG levels remained high in three patients until just before death. Serum TBG level dropped in one patient after an operation for gastric cancer. Thus, 8/169 cancer patients had high serum levels of TBG without apparent cause. The use of TBG as a tumor marker is suggested. (18 Refs)

42. COMPLEX IN VIVO AND IN VITRO RADIODIAGNOSIS OF THYROID CANCER.

Ivanov PK
Inst. Clinical Oncology, All-Union Cancer Res. Center, Moscow, USSR
Med Radiol (Mosk); 27(6):32-38 1982

Diagnostic efficacy of complex radionuclide and radiographic examination was evaluated in 237 patients with various nodular formations in the thyroid and/or in the neck. Among these patients, 68 had thyroid carcinoma, 59 had thyroid adenoma, 33 had nodular goiter, 20 had thyroiditis, 17 had thyrotoxicosis, 5 had diffuse goiter, and 35 had neck nodules without palpable thyroid nodules. Thyroid scintigraphy showed the presence of 'cold' nodule in 84% of the patients with thyroid carcinoma and in approx 50% of the patients with benign thyroid formations. Computer tomography was effective in diagnosis of occult thyroid cancer. Diagnostic efficacy of thermography in the patients with 'cold' nodules was 72.9%. Radioimmunoassay of thyroid hormones in the patients with thyroid cancer showed marked decrease of the blood level of thyroxine (61.7 units, compared with 97.12 units in the patients with thyroid adenoma) and increase of thyrotropin level (12.6 units, compared with 5.0 units in thyroid adenoma). The sensitivity of thyroxine and thyrotropin assays was 81.4% and 88.7%, respectively. Antibodies against thyroglobulin were specific markers of chronic thyroiditis. (4 Refs) (In RUS)

43. THE ENDOCRINE SYSTEM IN WHOLE-BODY HYPERTHERMIA.

Burmeister P, Neumann H, Fabricius H, Engelhardt R
Abt. Klinische Endokrinologie, Med. Univ.-Klinik Freiburg, Freiburg, W. Germany
Verh Dtsch Ges Inn Med; (87):633-637 1981

The effects of whole-body hyperthermia on the endocrine system were studied in 21 tumor patients and 11 healthy controls. The tumors included lymphogranulomatosis, Hodgkin's disease, squamous epithelial carcinoma, and small-cell bronchogenic carcinoma. The hyperthermia was induced with a microwave apparatus. A rectal temperature of 40 C was attained within 30-40 min and maintained for greater than 60 min. Blood samples were obtained at different times: before induction of hyperthermia, at the time the rectal temperature reached 40 C, after 1 hr at 40 C, and 24 hr later. During hyperthermia, increases in plasma levels of ACTH (measured only in controls), hydrocortisone, and prolactin were found. Somatotropic hormone (STH) levels increased in the controls and then declined during the hyperthermic phase to normal levels at 24 hr; no increase was noted in the tumor patients. In both groups insulin levels fell during hyperthermia and rose on the following morning, while glucagon levels rose during hyperthermia and were low on the following morning. Aldosterone increased significantly towards the end of the hyperthermic phase. No significant changes in values were found for follicle-stimulating hormone, luteinizing hormone, testosterone in men, thyroid-stimulating hormone, thyroxin, triiodothyronine, gastrin, parathormone, or C-peptide. The hyperthermia was evidently a strong stimulus to the endocrine system. The only significant difference between the response of the tumor patients and that of the controls was exhibited by the STH. (3 Refs) (In GER)

44. BLOOD PLASMA LEVELS OF HORMONES AND CARCINOEMBRYONIC ANTIGEN IN TUMOR AND NON-TUMOR DISEASES OF THYROID.

Ivanov PK, Tkacheva GA
Center Oncology Res., USSR Acad. Medical Sciences, Moscow, USSR
Vopr Onkol; 28(4):29-34 1982

Radioimmunological tests for carcinoembryonic antigen, antibodies to thyroglobulin, thyrotropin of pituitary, thyroxin and triiodothyronine were run in healthy subjects and patients suffering from cervical thyroid and extrathyroid neoplasms, eg nodular goiter, adenoma, cancer, chronic thyroiditis, lymphadenitis, neurinoma, hemangioma and thyrotoxicosis. The thyroid was scanned with 131I or 99mTcO4 in all cases. Scanning of thyroid is the first stage of screening for malignant tumors because 'warm' or 'hot' foci in scanograms of cases of malignant nodes are very rare. In patients with 'cold' thyroid nodes, detection of thyroglobulin antibodies points to thyroiditis since such antibodies are not found in all other cases. None of the indices showed any differences in cases of nodular goiter and 'cold' adenoma. Coefficient sTTH/bTTH (ratio of thyroliberine-stimulated level of pituitary thyrotropin to basal one) is decreased, while coefficient BTTH/T4, BTTH/IFT4 and blood plasma level of carcinoembryonic antigen are increased in patients with thyroid cancer as compared with benign tumors. (Author abstract) (10 Refs) (In RUS)

45. EVALUATION OF LONG-TERM SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) (MEETING ABSTRACT).

Nesbit M, Robison L, Sather H, Meadows A, Ortega J, Hammond D
Childrens Cancer Study Group (CCSG), Los Angeles, CA, 90031
Proc Am Assoc Cancer Res; 23:419 1982

CCSG (Childrens Cancer Study Group) initiated a study designed to evaluate a cohort of long-term survivors of childhood ALL to determine the possible occurrence of adverse effects of therapy. Patients were diagnosed between 1972 and 1974. Thus far 198 patients have been fully or partially evaluated for thyroid function, gonadal function, stature, formation of cataracts and the occurrence of second cancers. A marked decrease (p less than 0.001) in height was observed in both sexes. Forty-eight percent of the 189 patients were below the 25th percentile for height. Of the 97 patients evaluated for thyroid function, 12% demonstrated an elevated thyroid stimulating hormone (TSH) level with a normal thyroxine (T4) and triiodothyronine (T3) resin uptake and an additional 2% of the patients had primary hypothyroidism. Three patients have developed second malignant neoplasms (brain stem glioma, reticulum cell sarcoma, thyroid carcinoma). With 4,555 person years of followup, this represents a 5.3 fold increase over what would be expected in the general population. Six percent of the patients (3/50) demonstrated the presence of small posterior cataracts upon slit lamp examination. Of the 58 females evaluated 45% had elevated levels of serum follicle stimulating hormone (FSH) indicating ovarian failure. The proportion with elevated serum FSH was significantly higher in those who received spinal radiation as compared to those who did not (p greater than 0.001). In contrast only 4 (12%) of the 33 males evaluated had increased levels of serum FSH. The preliminary results of this ongoing study indicate that children and young adults successfully treated for ALL are subject to development of adverse late-effects. However, the proportion of patients affected and the seriousness of these complications are far outweighed by the marked improvement in survival. (no Refs)

46. HYPERCALCEMIA IN HEAD AND NECK CARCINOMA: INCIDENCE, ETIOLOGY, AND PROGNOSIS (MEETING ABSTRACT).

Won C, Decker DA, Drelichman A, Al-Sarraf M, Reed ML
Wayne State University, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:602 1982

A retrospective review of all head and neck cancers seen between January 1, 1975 and September 1, 1981 at Harper-Grace Hospital was performed. Of 1438 head and neck cancers, 41 had hypercalcemia during the course of their disease. Ages ranged from 17-80 years, mean 56 years. The incidence of hypercalcemia by site was 13/351 larynx, 7/280 pharynx, 19/733 oral cavity (floor of mouth 4/171, tongue 9/209, tonsil 5/176, palate 1/95, other 0/82), 2/26 nasal cavity, 0/48 salivary gland carcinomas. Of the 41 patients with hypercalcemia, 40 had squamous cell carcinomas (SCC) and one undifferentiated carcinoma. Of the SCC, 9 were poorly differentiated, 15 moderately differentiated, 4 well differentiated, and 12 not specified. Time from diagnosis of cancer to first diagnosis of hypercalcemia ranged from 0-1440 days, mean 191 days. Thirty-seven had Stage IV and four Stage III. Chest radiographs were positive for mass lesions in 17/41. Bone scans of metastatic bone surveys were positive in 13/41, negative in 16/41, and not evaluable in 12. Five had serum PTH (parathyroid hormone) level performed and in all five the PTH level was inappropriately elevated for the serum calcium level, suggesting ectopic PTH production. The hypercalcemia was medically treated in 29/41, successfully with a return to normal calcemia levels in 17/29. Twelve patients received only palliative care. Survival from the first diagnosis of hypercalcemia ranged from 1-514 plus days, mean 80 days, median 33 days. (no Refs)

47. TOPICAL DIAGNOSIS OF CHROMAFFIN TUMORS BY DETERMINATION OF CATECHOLAMINE LEVEL IN PLASMA SAMPLES.

Iurginov OG, Komissarenko IV, Bezverkhaia TP, Makarenko GI
Res. Inst. Endocrinology and Metabolism, Kiev, USSR
Probl Endokrinol (Mosk); 28(3):24-29 1982

Diagnostic efficacy of selective determination of plasma levels of epinephrine (E) and norepinephrine (NE) was studied in 10 patients with chromaffin tumors. Blood samples were withdrawn from renal and adrenal, veins, inferior vena cava, right atrium, and superior vena cava. Of 10 patients, 6 had unilateral increase of catecholamine levels in the blood from the adrenal veins: 5 patients were found to have pheochromocytoma of the left adrenal and 1 had pheochromocytoma of the right adrenal. Of two patients with bilateral pheochromocytomas, one had 2-5.5x increase of E and NE levels in the blood from the right and left adrenal veins. The second patient with bilateral pheochromocytomas had relatively even increase of basal catecholamine levels in all regions with 8x and 10x increase of E and NE levels, respectively, in the right adrenal vein, compared with those in the left adrenal vein. Two patients with extra-adrenal tumors (pararenal paraganglioma and bladder pheochromocytoma) had marked elevation of E and NE in the blood from the inferior vena cava. (23 Refs) (In RUS)

48. DIAGNOSIS AND TREATMENT OF PHEOCHROMOCYTOMA.

Serniak PS, Denisov VK
Dept. Urology and Surgical Nephrology, A. M. Gorky Medical Inst., Donetsk, USSR
Urol Nefrol (Mosk); (3):3-6 1982

Of 16 patients with adrenal tumors, 11 had pheochromocytomas, 2 had adenomas, 2 had cysts, and 1 had immature tumor. Clinical manifestations of pheochromocytoma included paroxysmal elevation of blood pressure, sharp headache and chest pain, vertigo, nausea and vomiting, and paresthesias. Of 11 patients with pheochromocytomas, 3 had paroxysmal hypertension while 8 had persistent hypertension without pronounced crises. The most accurate method of diagnosis of pheochromocytoma in the patients without paroxysms of hypertension was determination of the urinary excretion of catecholamines. Additional diagnostic methods included pressor and depressor tests and x-ray examination (excretory urography, retropneumoperitoneum, and aortography). Surgery was the treatment of choice. Intraoperative infusion of norepinephrine and corticosteroids prevented severe or even fatal shock caused by the critical drop of the blood pressure. Surgery was performed in 8/11 patients. Two patients had bilateral pheochromocytomas. (6 Refs) (In RUS)

49. TOLBUTAMIDE AND SOMATOSTATIN TESTS IN THE DIAGNOSIS OF INSULINOMA.

Jara Alberran A, Caballero Asensi A, Garcia Peris P, Coste A, Toledano E, Gorospe C, Caviola E, Palacios Mateos JM
Servicio de Endocrinologia y Laboratorio de RIA, Hospital Oncologico, Madrid, Spain
Rev Clin Esp; 164(2):105-109 1982

Tolbutamide (Ta: 1 g iv) and Ta plus somatostatin (500 ug in a 60-min infusion) tests were performed in two patients with hypoglycemia due to insulinomas and in two with functional hypoglycemia. Somatostatin was found to inhibit the response to tolbutamide in the patients with functional hypoglycemia but not in those with insulinomas. This phenomenon disappeared after removal of the insulinomas. It is concluded that the tolbutamide-somatostatin test may be useful in the diagnosis of insulinoma when other diagnostic methods do not yield clear results. (16 Refs) (In SPA)

50. LOCALIZATION OF THE SOURCE OF HYPERINSULINISM: PERCUTANEOUS TRANSHEPATIC PORTAL AND PANCREATIC VEIN CATHETERIZATION WITH HORMONE ASSAY.

Cho KJ, Vinik AI, Thompson NW, Shields JJ, Porter DJ, Brady TM, Cadavid G, Fajans SS
Dept. Radiology, Univ. Michigan Medical Center, Ann Arbor, MI, 48109
AJR; 139(2):237-245 1982

Insulin concentrations were measured in the portal venous system through the percutaneous transhepatic approach in 12 patients with organic hyperinsulinism. Single insulinomas were found in 10, an adenoma and islet cell hyperplasia in one, and nesidioblastosis in one patient. Angiography localized adenomas in two. Local step-ups of insulin levels in the portal venous system, found in all patients with insulinomas, corresponded to tumor sites at surgery. Multiple step-ups were found in the portal venous system of the patient with nesidioblastosis and the patient with an adenoma with islet cell hyperplasia. Three tumors were localized in the head of the pancreas which would dictate the primary surgical approach rather than blind resection of the body and tail. Three of the 10 adenomas were not identifiable by palpation after pancreatic mobilization during surgery. In all patients, organic hyperinsulinism was cured after surgery. Percutaneous transhepatic portal and pancreatic vein catheterization with measurement of radioimmunoactive insulin concentrations is a safe and reliable method and may play an important role in the localization of adenomas in patients with normal angiographic studies and previous negative surgical explorations. (Author abstract) (16 Refs)

51. ENDOCRINE FUNCTION OF THE PANCREAS IN PATIENTS WITH CANCER OF THE STOMACH SUBJECTED TO COMBINED TREATMENT WITH PREOPERATIVE GAMMA-THERAPY.

Vedzizheva TB, Berdov BA, Bassalyk LS, Gromova NV
Res. Inst. Medical Radiology, Obninsk, USSR
Med Radiol (Mosk); 27(6):11-14 1982

Effect of preoperative radiotherapy on the endocrine function of the pancreas was studied in 70 patients (50 men, 20 women; 33-77 yr old) with Stage II-IV cancer of the stomach. The patients received preoperative distance gammatherapy from two fields (400 rads/day, for 5 days, total dose 2,000 rads). The dose to the pancreas comprised of 80-90% of a total focal dose. The functional state of the pancreas was evaluated by the levels of immunoreactive insulin (IRI) and immunoreactive glucagon (IRG). Basal levels of IRI and IRG in the stomach cancer patients (14.4 and 78.0 units, respectively) did not differ from those in healthy controls (16.7 and 69.6 units, respectively). The av levels of IRI and IRG on day 3 after irradiation were 14.9 and 94.9 units, respectively. Preoperative radiotherapy produced an increase of IRI in the patients with low basal IRI and elevated basal IRG, compared with significant decrease of IRI level in the patients with normal basal levels of IRI and IRG. (6 Refs) (In RUS)

52. CHEMOTHERAPY OF ISLET CELL CARCINOMA WITH CHLOROZOTOCIN (CTZ): A SOUTHWEST ONCOLOGY GROUP STUDY (MEETING ABSTRACT).

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Cleveland Clinic Foundation, Cleveland, OH, 44106

Proc Am Soc Clin Oncol; 1:C-349 1982

CTZ is a nitrosourea having structural features in common with streptozotocin (STZ). In view of the activity of STZ in islet cell carcinoma, a phase II trial of CTZ in this neoplasm was initiated in 1979. Nineteen patients were registered, and 17 are evaluable for response and toxicity. Median age was 56 years and the male/female ratio was 9/8. All patients had objectively measurable tumor masses, and 8 had functioning tumors (gastrin 4, insulin 2, vasoactive intestinal polypeptide 2). Eleven patients were previously untreated, 2 had received prior x-ray therapy, and 4 prior chemotherapy (STZ in all instances). CTZ was administered as an IV bolus q6wks at the dose levels of 100 and 200 mg/m2. Six of 17 patients responded, and 1/17 patients demonstrated a minor tumor regression. All responses consisted of objective tumor regressions and a greater than or equal to 50% decrease in the secretory product if present (3 patients). In patients receiving no prior chemotherapy 6/13 (46%) responded. Median response duration was 4+ mos, and median survival has not yet been reached. Toxicity included leukopenia in 9/17, thrombocytopenia in 5/17, and mild nausea and vomiting in 5/17. Renal toxicity in the form of an elevated blood-urea nitrogen and/or creatinine occurred in 3/17 patients, and developed in 1 instance 6 mos following discontinuation of CTZ. The activity of CTZ appears comparable to STZ, with substantially less gastrointestinal toxicity. (no Refs)

53. CALCITONIN IMMUNOREACTIVE PROTEIN, A TUMOR MARKER IN SMALL-CELL BRONCHOGENIC CARCINOMA.

Luster W, Gropp C, Havemann K

Abt. fur Hamatologie und Onkologie, Med. Klinik, Marburg, W.Germany

Verh Dtsch Ges Inn Med; (87):1089-1092 1981

Calcitonin was measured in the serum of 152 patients with lung tumors of various histological types. Protein molecules showing calcitonin activity were characterized by column chromatography. Small-cell bronchogenic carcinoma produced such molecules in proportion to the synthetic capacity of the cells. These molecules probably represent precursors of calcitonin and are suited to use as markers for monitoring and guiding therapy of small-cell carcinoma. (8 Refs) (In GER)

54. ACTH AND CALCITONIN AS TUMOR MARKERS IN PATIENTS WITH LEUKEMIA.

Pfluger KH, Gropp C, Gramse M, Havemann K

Abt. fur Hamatologie und Onkologie, Med. Klinik Marburg, Marburg, W. Germany

Verh Dtsch Ges Inn Med; (87):1096-1100 1981

The incidence of elevated serum levels of calcitonin (CT) and ACTH was studied in patients with malignant hemoblastoses; proteohormone molecules were isolated and characterized. Radioimmunoassays were performed on samples of peripheral venous blood and extracts of leukemia cells and tissue samples. Elevated levels of CT greater than double the normal value were found in 46.5% of patients with acute leukemia. Approx 20% of these patients had levels greater than 1,000 picog/ml. The incidence of elevated serum CT was lower in patients with chronic leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma. No significant differences were found between different types of acute leukemia. Elevated levels of ACTH were found in only 5% of patients with acute leukemia or blast crisis of chronic leukemia. Of three patients with elevated ACTH levels, one had clinically diagnosed Cushing's syndrome; blood sugar and cortisol levels normalized after 4-5 mo of therapy. ACTH levels did not normalized during further therapy. The patient formed autoantibodies against the immunoreactive ACTH. Two types of ACTH molecule, possibly precursors of ACTH, with mol wt of 30,000-35,000 daltons were identified. Immunoreactive CT molecules with mol wt of 10,000-20,000, 45,000, or 60,000 daltons were identified. Whether these molecules represent precursors of CT or specific or nonspecific protein complexes is not known. Findings indicate that immunoreactive ACTH and CT are found in leukemia cells and are probably produced there. CT is a suitable marker for monitoring leukemia therapy and detecting recurrence. (13 Refs) (In GER)

55. PARANEOPLASTIC ACTH SECRETION IN PATIENTS WITH BRONCHOGENIC CARCINOMA IN THE DEXAMETHASONE TEST.

Allolio B, Winkelmann W, Brosch H, Hipp FX, Schroder B

Med. Klinik, Krankenhaus Koln-Merheim, Koln, W. Germany

Verh Dtsch Ges Inn Med; (87):637-640 1981

ACTH secretion before and after administration of dexamethasone was measured in 108 patients with bronchogenic carcinoma and in 30 controls with benign lung disease. Abnormally high ACTH secretion that was not suppressed by the dexamethasone treatment was found in 38% of the patients with small-cell bronchogenic carcinoma, 11% of those with polymorphic-cell carcinoma, and 43% of those with adenocarcinoma. Among the patients with benign lung disease or those with squamous epithelial or alveolar-cell carcinoma, ACTH secretion was suppressed by the dexamethasone. The dexamethasone test for ectopic ACTH secretion was considered to be useful for diagnosis and monitoring of patients with bronchogenic carcinoma. (5 Refs) (In GER)

56. NORMAL SERUM 1,25-DIHYDROXYVITAMIN D IN PATIENTS WITH MEDULLARY CARCINOMA OF THE THYROID.

Lee S, Morimoto S, Onishi T, Tsuji M, Okada Y, Seino Y, Ishida M, Yamaoka K, Takai S, Miyauchi A, Kumahara Y
Dept. Medicine and Geriatrics, Osaka Univ. Medical Sch., Fukushima-ku, Osaka, Japan
J Clin Endocrinol Metab; 55(2):361-363 1982

Serum calcium, phosphorus, calcitonin, parathyroid hormone, 25-hydroxyvitamin D (25OHD), and 1,25-dihydroxyvitamin D [1,25-(OH)2D] were measured in 6 women and 2 men with medullary carcinoma of the thyroid, 22 normal subjects, 5 patients with chronic renal failure, and 5 patients with primary hyperparathyroidism. Serum 1,25-(OH)2D levels were significantly higher in patients with primary hyperparathyroidism and lower in patients with chronic renal failure than in normal subjects. In patients with medullary carcinoma of the thyroid, the serum calcitonin levels were elevated, but the parathyroid hormone and 1,25-(OH)2D levels were within normal ranges. The serum 25OHD levels were not significantly different in any group. It is concluded that chronic elevation of serum calcitonin has no effect on the serum 1,25-(OH)2D level. (Author abstract) (18 Refs)

57. ECTOPICALLY PRODUCED CALCITONIN IN HUMAN HEMOBLASTOSES.

Pfluger KH, Gropp C, Havemann K
(c/o Havemann) Abt. Hamatologie, Med. Univ.-Klinik, Mannkopffstr., D-3550 Marburg, W. Germany
Klin Wochenschr; 60(13):667-672 1982

The incidence of elevated serum levels of immunoreactive calcitonin (CT) in human myeloproliferative and lymphoproliferative disorders was investigated. On the basis of twice the normal range, about 45% of patients with acute leukemia and blast crisis of chronic myelocytic leukemia (CML) showed elevated serum levels of CT. Markedly elevated levels (greater than 1,000 pg/ml) were only found in this group. Since immunoreactive CT dropped to normal or only slightly elevated levels in remission and increased again before or during relapse, serum CT levels seem to reflect the activity of the disease. However, in patients with chronic leukemia, Hodgkin's and non-Hodgkin's lymphoma, a lower incidence and only slightly elevated serum values were found. In addition, the mol wt of the proteohormone in serum specimen and cell extracts was investigated by gel chromatography. Besides physiological CT, different high-mol wt forms of the hormone could be demonstrated in serum and in cell extracts. Extracts of leukemic cells revealed higher molecular forms only. It is suggested that the proteohormone is ectopically produced by leukemic cells. (Author abstract) (27 Refs)

58. ANAEMIA IN PATIENTS WITH MYELOMATOSIS.

Ting WC, Cavill I, Jacobs A, Kaaba S, May A, Smith S, Whittaker JA
(c/o Jacobs) Dept. Haematology, Welsh Natl. Sch. Medicine, Heath Park, Cardiff CF4 4XN, Wales
Br J Cancer; 45(6):887-894 1982

Twenty-four untreated patients with myelomatosis were studied in order to characterize their anemia, using standard hematological and ferrokinetic techniques, together with measurements of circulating erythropoietin, erythropoietin sensitivity of marrow cultures and in vitro measurements of heme synthesis. There is a reduction in total erythroid output by the marrow, together with a minor degree of plasma expansion. In patients with normal renal function there is an appropriate increase in erythropoietin in response to anemia, but in a few cases there may be reduced response of CFU-E to the hormone in vitro. No abnormality of iron status or heme synthesis was found. One case of folate deficiency was discovered. (Author abstract) (30 Refs)

59. EVIDENCE OF A HEMATOPOIETIC EFFECTIVE FACTOR IN SERUM OF PATIENTS WITH POLYCYTHEMIA VERA.

Hellmann E, Holzknecht A, Fahrenkrug H
Med. Poliklinik Munster, Munster, W. Germany
Verh Dtsch Ges Inn Med; (87):772-775 1981

Possible involvement of a serum factor in polycythemia vera (PV) was studied. Hematopoietic stem cells were obtained from the peripheral blood of normal individuals. The stem cells were cultured with serum from patients with PV in the presence or absence of erythropoietin (EP). PV serum significantly increased the number of colony-forming units and blast-forming units. The increase was greater in the presence of EP than in the absence of EP. Results support the belief that a serum factor is involved in abnormal hematopoiesis in PV. (10 Refs) (In GER)

60. THYMOSIN ALPHA1 FOLLOWING MEDIASTINAL IRRADIATION: AN IMMUNO-RESTORATIVE TRIAL IN PATIENTS WITH LOCALIZED NON-SMALL CELL LUNG CANCER (MEETING ABSTRACT).

Schulof RS, McClure JE, Goldstein AL, Cohen P
Departments of Medicine and Biochemistry, George Washington University Medical Center, Washington, DC, 20037
Proc Am Soc Clin Oncol; 1:C-133 1982

A double blind randomized phase I/II trial of synthetic thymosin alpha 1 was performed in patients with non-metastatic, non-small cell lung cancer who had just completed mediastinal irradiation (RT). The trial was designed to determine whether parenteral (SQ) alpha 1 (900ug/m(2)) administration could accelerate the reconstitution of thymic dependent immunity following RT. To date, 22 patients have been randomized into 3 groups: 1) intensive alpha 1; daily x 14 followed by twice a week maintenance, 2) alpha 1 twice a week, 3) placebo twice a week. Treatment was begun within a week after completion of RT and continued for one year or until relapse. RT resulted in: 1) a significant depression of peripheral blood lymphocytes/mm3 expressing E-rosette receptors or OKT3 antigen; 2) a depression of T-cell proliferative responses in mixed lymphocyte culture (T-MLC); 3) an augmentation of OKT4/OKT8; and 4) no change in %E-RFC, or in Tu/Tgamma. In vitro incubation with alpha 1 could partially restore T-MLC in 30-40% of patients with post-RT values below the mean of age matched normals. Following SQ injection, serum alpha 1 levels peaked at 25-30 ng/ml by 6 hours and returned to near baseline by 24 hours. Patients receiving alpha 1 maintained higher baseline alpha 1 levels than those receiving placebo. With a mean follow-up period of 22 weeks, one of the treatment arms exhibited a greater percentage of relapses (6/7) than the other two (2/7 and 3/6). However, no significant trends could be identified in the recovery of T-cell numbers or function among the groups. (no Refs)

61. PHASE I TRIALS OF THYMOSIN FRACTION 5 (TF5) AND THYMOSIN ALPHA (TA1) AND ASSESSMENT OF IMMUNOLOGIC RESPONSE (MEETING ABSTRACT).

Dillman RO, Beauregard JC, Zavanelli MI, Halliburton BL, Royston I
University of California, San Diego Cancer Center, School of Medicine, San Diego, CA, 92161
Proc Am Soc Clin Oncol; 1:C-166 1982

TF5 and TA1 were tested as part of the Biological Response Modifiers Program. Seventy-two patients with advanced cancer were screened for immunosuppresion using a battery of cell surface markers and lymphocyte function assays. Marker studies included proportion and number of lymphocytes, T cells by E-rosettes and monoclonal antibodies, helper and suppressor cells and Ia+ cells by monoclonal antibodies, B cells by surface immunoglobulin. Functional assays included phytohemagglutinin, concanavalin-A, pokeweed mitogen, one-way mixed lymphocyte reactions to human lymphocytes and cell lines, and response to viral antigen (varicella-zoster). As a group, cancer patients had statistically lower means for 16/21 in vitro tests of immunosuppression as compared to healthy controls. Over 2/3 of cancer patients were determined to be immunosuppressed. The ratio of helper/suppressor cells was less than 1:1 in half of the cancer patients, but in less than 10% of controls. Twenty-two patients received 30 courses of single intramuscular injections of TF5 or TA1 according to a doubling dose escalation schedule. Such patients were tested on 3 occasions before receiving thymosin, then daily X 3 and weekly X 3 after the injection. Results can be summarized as follows: (1) TF5 and TA1 were well tolerated over the dose range of 60-480 mg/m2 and 600 ng to 9.6 mg/m2 respectively; (2) any effects of TF5 or TA1 on various assays were seen within 24-48 hours and did not persist beyond 72 hours; (3) there was marked variation in terms of immune response; and (4) no dose-response correlation was apparent. (no Refs)

EFFECTS ON NORMAL AND NEOPLASTIC CELLS AND TISSUES

62. GROWTH RESPONSES OF RAT STOMACH CANCER CELLS TO GASTRO-ENTERO-PANCREATIC HORMONES.

Kobori O, Vuillot MT, Martin F
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Int J Cancer; 30(1):65-67 1982

Various hormones and peptides were added to rat stomach cancer cells growing in vitro in a serum-free medium and the cell number was determined by a spectro-photometric method. Five gastro-entero-pancreatic hormones or related peptides (tetragastrin, glucagon, secretin, cholecystokinin-pancreozymin and cerulein) significantly increased the number of stomach cancer cells from 150% to 310% of the number of control cells cultivated in a serum-free, hormone-free medium. On the other hand, insulin and vasoactive intestinal peptide, and other hormones (thyroxin, epinephrine, hydrocortisone, beta-estradiol, progesterone, testosterone), peptone broth and bovine serum albumin had no significant growth effect. All the active substances belong to the two major families of gastro-entero-pancreatic polypeptide hormones, suggesting the existence of hormone receptors at the surface of stomach cancer cells. (Author abstract) (10 Refs)

63. ALTERATIONS OF GLIAL TUMOR CELL CA2+ METABOLISM AND CA2+-DEPENDENT CAMP ACCUMULATION BY PHORBOL MYRISTATE ACETATE.

Brostrom MA, Brostrom CO, Brotman LA, Lee CS, Wolff DJ, Geller HM
Dept. Pharmacology, Rutgers Medical Sch., Univ. Medicine and Dentistry New Jersey, Piscataway, NJ, 08854
J Biol Chem; 257(12):6758-6765 1982

C6 glial tumor cells exposed to phorbol myristate acetate (PMA) possessed lowered cAMP content, reduced ability to accumulate cAMP in response to norepinephrine or cholera toxin, and a three-fold increase in the concentration of norepinephrine producing 50% of the maximal rate of cAMP accumulation. Detectable effects on cAMP accumulation occurred within 10 min of exposure to PMA, and prominent effects by 2 hr. PMA similarly affected cells pretreated with cycloheximide. In contrast, Ca++-depleted preparations of control and PMA-treated cells accumulated cAMP identically in response to norepinephrine or cholera toxin. Ca++ restoration, which increased the rate of cAMP accumulation in control cells severalfold, did not enhance cAMP accumulation in PMA-treated cells. Neither high catecholamine nor high extracellular Ca++ concentrations reversed the suppression of cAMP accumulation by PMA. Trifluoperazine, which inhibited the Ca++-dependent component of norepinephrine-stimulated cAMP accumulation in control cells, did not significantly reduce norepinephrine-stimulated cAMP accumulation in PMA-treated cells. Cell-free preparations of control and PMA-treated cultures did not differ significantly in calmodulin content or in Ca++-stimulated adenylate cyclase, Ca++-dependent cAMP phosphodiesterase, and (Ca++-Mg++)-ATPase activities. The Ca++ content, however, of intact cells decreased with time of PMA treatment. Within minutes after exposure to PMA, the ability of Ca++-depleted cells to take up 45Ca was significantly reduced. Both 45Ca uptake and Ca++-dependent cAMP accumulation were reduced over the same PMA concentration range. (Author abstract) (34 Refs)

64. CYTOLOGICAL STUDY ON THE ANTERIOR PITUITARY OF SENILE UNTREATED BEAGLE BITCHES WITH SPONTANEOUS MAMMARY TUMOURS.

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Arch Toxicol; 50(1):35-45 1982

Pituitaries were obtained from senile untreated Beagle bitches of comparable age (7-9 yr) and genital status. The animals were divided into three groups; one was normal (without mammary lesions), one had benign tumors and one had mammary adenocarcinomas. PRL-, STH-, ACTH- and gonadotrophin-producing cells are studied and counted in serial paraffin sections stained with histochemical techniques. The animals with mammary malignancy displayed a marked increase in the relative number of PRL and ACTH cells with morphological signs of higher secretory activity in most cells, compared with that in normal bitches or bitches with benign tumors. STH cells in bitches with adenocarcinomas were reduced in number; however the secretory activity in these animals was the same as that observed in the normal bitches. In the animals with benign mammary tumors, STH cells showed morphological indication of higher secretory activity than in the other groups. PRL and ACTH cells were slightly increased in number and had slightly higher activity than that in normal bitches. These findings may suggest a role for hypophyseal hormones in mammary neoplasias. (Author abstract) (18 Refs)

65. RESPONSE OF VASCULAR PERMEABILITY IN INTRAHEPATIC TUMORS TO STEROIDAL AND NON-STEROIDAL ANTI-INFLAMMATORY AGENTS (MEETING ABSTRACT).

Ackerman NB, Makohon S
Upstate Medical Center, Syracuse, NY, 13210
Proc Am Assoc Cancer Res; 23:167 1982

Previous studies in this laboratory have demonstrated increased vascular permeability in Walker carcinosarcomas implanted within the liver of Sprague-Dawley rats compared to permeability in the host liver tissue. The present studies were designed to determine whether the tumor vasculature will respond to the anti-inflammatory effects of steroids and non-steroidal agents with measurable decreases in permeability. All drugs were injected in a bolus directly into the celiac artery, followed by intravenous administration of Evans blue. Rats were sacrificed at 5 min, 30min and 6 hours and dye was extracted from tumor and liver samples. Permeability activity was determined by spectrophotometric measurement. All steroids tested (hydrocortisone, methyl-prednisolone, and triamcinolone) significantly decreased tumor vascular permeability at all time periods liver vascular permeability was more variably affected by these drugs. Non-steroidal agents (indomethacin, phenylbutazone, ibuprofen and naproxan) produced similar effects on tumors; naproxan also appeared to decrease hepatic vascular permeability. Epinephrine lowered tumor vascular permeability without affecting the liver. Vascular permeability of newly formed tumor vessels resembles that within inflammatory tissues, and increases only with physical changes produced by extreme hypothermia and hyperthermia, but does not respond further to agents such as histamine. The tumor vessels appear to respond to anti-inflammatory agents with a significant decrease in vascular permeability. (no Refs)

66. METABOLIC CONTROLS AND CELLULAR RESPONSE TO DRUGS AND RADIATION (MEETING ABSTRACT).

Biaglow JE
Department of Radiology, Case Western Reserve University, Cleveland, OH, 44106
Program and Abstracts of the 6th Annual Meeting of the Cell Kinetics Society, March 19-21, 1982, Houston, Texas. The Cell Kinetics Society 38 pp., 1982.

There is a great deal of interest in understanding the response of different tumor cell populations to drugs and radiation. These populations may vary in their position in the cell cycle, may be nutritionally deprived and may contain cells in both acute and chronic hypoxic states. Obviously, it is too complicated to define the response of all of these different cell populations within a tumor to a particular agent. Therefore, we have attempted to establish in vitro cell models which may mimic some of the conditions believed to exist in vivo. We have been concerned with oxygen tension, alterations in rates of cellular oxygen utilization, enzyme adaptation and changes in nonprotein thiols that occur as a cell enters into the so called Go or nongrowing state. In addition, the mitogenic effect of insulin and nutrients on reentrance of the cells into the growth phase has also been investigated as a means for enhancing the response to radiation and drugs. (no Refs)

67. ENDOGENOUS HORMONES AS A MAJOR FACTOR IN HUMAN CANCER.

Henderson BE, Ross RK, Pike MC, Casagrande JT
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Cancer Res; 42(8):3232-3239 1982

Hormone-related cancers account for almost 30% of all cancer cases in the United States. Data from animal experiments and from epidemiological and endocrinological studies in humans support the hypothesis that the individual hormones which control normal growth of target organs can also create the proper conditions for neoplastic transformation. The concept that hormones can cause, ie, increase the incidence of, human cancer is most developed for the four hormone-related cancers which are numerically the most important, namely, breast, prostate, endometrium, and ovary. Even for these sites, large gaps remain in our knowledge of the responsible hormones and the conditions which create the optimal opportunity for carcinogenesis. Although scanty, the available epidemiological evidence also suggests a hormonal role in the pathogenesis of testis cancer, thyroid cancer, and osteosarcoma. We believe that the primary prevention of all these cancers will probably depend on modification of the factors which affect the secretion and metabolism of the responsible hormones rather than on control of exposure to classical exogenous initiators. (Author abstract) (129 Refs)

68. RESISTANCE OF TERMINAL DIFFERENTIATION IN PRECANCEROUS MAMMARY HYPERPLASIA (MEETING ABSTRACT).

McGrath CM, Soule HD
Michigan Cancer Foundation, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:904 1982

Acquired resistance to terminal differentiation is a crucial step in neoplastic transformation of cells that grow by differentiative renewal (eg mammary cells). We sought to determine if such resistance was already acquired at the precancerous stage of mammary cell transformation, and if it was associated with new responsivity to hormones normally controlling proliferation. Hyperplastic ductal and alveolar foci, induced by DMBA (dimethylbenzanthracene) and oncogenic viruses respectively, were isolated from Balb/c mouse mammary glands. Cells were pseudocloned from individual atypias on collagen-coated substrates and tested for accumulation of casein (a marker for end-point differentiation) in response to insulin (I), cortisol (F) and prolactin (M). Responsivity of differentiation-resistant and sensitive cells to mitogens was determined by replica plating corresponding colonies. Persistant precancerous hyperplasias, both ductal and alveolar, but not benign involutional hyperplasias, contained reduced numbers of cells responsive to IFM, when compared to normoplastic controls. Results of replica plating experiments in which proliferative responsivity of cells to epidermal growth factor (EGF) was measured autoradiographically, suggest that cells resistant to terminal differentiation are also more responsive to EGF. (no Refs)

69. EFFECT OF THYMOSIN FRACTION V ON HUMAN BONE MARROW AND BLOOD CELLS FROM NEWLY DIAGNOSED ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) PATIENTS (MEETING ABSTRACT).

Narula N, Miller DR, Meyers PA, Pahwa R
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Proc Am Soc Clin Oncol; 1:C-161 1982

Incubation of normal bone marrow lymphocytes (BML) and peripheral blood lymphocytes (PBL) with thymosin Fraction V (Fr V) results in an increase of certain T-cell markers. In the present study, we investigated the influence of thymosin Fr V on certain surface markers and functions of leukemic cell populations. Ficoll-Hypaque-separated BML and PBL (comprised of greater than 95% blasts) from 24 patients with ALL (3 of T-cell origin and 21 of non T-non B or Null cell type) were incubated with 25 ucg and 100 ucg of thymosin Fr V for 15 hours. The cells were washed and tested for induction of receptors for peanut agglutinin (PNA), rosette formation with sheep erythrocytes (E-R), surface antigens using monoclonal anti-Ia and anti-T cell (HuLyt 1, HuLyt 2, and HuLyt 3) antibodies and proliferative responses to mitogens phytohemagglutinin, concanavalin A, and pokeweed. Induction of PNA receptors was noted in PBL and BML in one patient and of E-R receptors in four patients. Marked heterogeneity was noted in the expression of Ia and Lyt antigens on the leukemic cells. With thymosin Fr V induction of one or more Lyt antigens occurred in cells of 3 patients (null-ALL). Functional activity was lacking in cells of all patients, and no change was noted after exposure to thymosin. Blasts cells from one patient were lacking in E-rosette forming capacity, while expressing the HuLyt 3 antigen, thus indicating a dissociation between these two markers. This study indicates that T as well as Null cell leukemias as defined by conventional tests can be potentially subclassified on the basis of additional surface markers, and that thymosin Fr V can induce certain T cell markers in so called 'null' type of leukemic cells. (no Refs)

EFFECTS OF ENDOGENOUS AND EXOGENOUS AGENTS ON NON-STEROID HORMONE ACTIVITY

70. MONENSIN INHIBITS CATECHOLAMINE SYNTHESIS IN PHEOCHROMOCYTOMA CELLS.

Vaccaro KK, Liang BT, Sheard BE, Perlman RL
(c/o Perlman) Dept. Physiology, Univ. Illinois Coll. Medicine, P. O. Box 6998, Chicago, IL, 60680
J Pharmacol Exp Ther; 221(3):536-540 1982

The carboxylic ionophore monensin was found to inhibit the activity of tyrosine 3-monoxygenase (TH) in transplantable rat pheochromocytoma cells. Monensin affected the conversion of tyrosine to catechols by first producing a 65% inhibition of the accumulation of catechols, then altering the pattern of catechol accumulation, causing dopamine to be the major catecholamine in treated cells. This effect could be explained by monensin's demonstrated inhibition of TH activity. To induce inhibition of TH, monensin treatment required the presence of extracellular sodium, while extracellular calcium was not necessary. The inhibitory effects of monensin upon TH were more pronounced in paraglyne-treated cells. Monenesin caused the release of norepinephrine from chromaffin granules isolated from pheochromocytoma cells. (21 Refs)

71. EFFECT OF HIGH-DOSE OESTROGEN ADMINISTRATION ON THE GROWTH AND PROLACTIN RECEPTOR CONTENT OF N-NITROSOMETHYLUREA-INDUCED MAMMARY TUMOURS IN THE RAT.

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J Endocrinol; 93(1):11-16 1982

The effect of chronic administration of a high dose of estradiol benzoate (OB) on growth and prolactin receptor content of the N-nitrosomethylurea (NMU)-induced rat mammary tumor was investigated. Daily im administration of 50 ug OB for 8 days to tumor-bearing rats induced marked reduction in tumor size which was already significant after only three injections. Simultaneous daily administration of 1 mg perphenazine to stimulate endogenous prolactin release counteracted the inhibitory effect on tumor growth of OB but only partially since the tumors grew significantly more when perphenazine was injected alone. No treatment significantly affected prolactin receptor content in the tumors. We concluded that administration of pharmacological doses of OB has a potent antitumor action on the NMU-induced rat mammary tumor. This effect can only partially be explained by inhibition of the peripheral action of prolactin. (Author abstract) (22 Refs)

72. THE EFFECT OF BROMOCRIPTINE ON RENIN, ALDOSTERONE AND KIDNEY FUNCTION IN PATIENTS WITH ACROMEGALY AND PROLACTINOMA.

Jungmann E, Albus M, Bottger B, Magnet W, Althoff PH
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Inn Med; 9(4):175-180 1982

Eleven patients with acromegaly and 4 with prolactinoma were given high dose therapy with bromocriptine (BC) over 1-5 yr. BC suppressed the aldosterone response to upright posture and furosemide and the furosemide-induced rise in plasma renin activity. BC increased cortisol and supine aldosterone levels in patients with normal renal function. BC decreased creatinine clearance (CC) to normal levels in patients with acromegaly and increased CC in patients with prolactinoma. In acromegaly BC improved adrenal function and CC by reducing levels of growth hormone. In prolactinoma BC increased CC by an adrenergic effect on renal perfusion. (15 Refs) (In GER)

73. THE PLACE OF BROMOCRIPTINE IN THE TREATMENT OF ENDOCRINE DISORDERS.

Althoff PH, Bottger B, Rosak C, Jungmann E, Neubauer M
Abteilung fur Endokrinologie, Zentrum der Inneren Medizin, Universitat Frankfurt am Main, Theodor-Stern-Kai, D-6000 Frankfurt/Main 70, W. Germany
Inn Med; 9(4):189-198 1982

Bromocriptine (BC) is a long-acting dopamine-agonist used in treatment of endocrinologic diseases of functional or organic origin. In patients with hyperprolactinemia chronic stimulation of dopamine-receptors by BC rapidly lowers serum prolactin level. Indications for BC therapy include acromegaly, prolactinoma, and idiopathic edema. Although BC apparently has no acute toxicity, numerous side effect may be produced by BC therapy. (13 Refs) (In GER)

74. EFFECTS OF ANTIBODIES TO CHORIOGONADOTROPIN IN MALIGNANT GROWTH. II. SOLID TRANSPLANTABLE RAT TUMORS.

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Cancer Immunol Immunother; 13(1):2-4 1982

Effects of preimmunization against choriogonadotropin (CG) were studied in two transplantable solid neoplasms, the R 3230 AC rat mammary adenocarcinoma and the 5123 1-1 rat hepatoma which have been shown to synthesize CG-like material. R 3230 AC rat mammary adenocarcinoma was maintained in Fischer 344 female rats, and the 5123 1-1 rat hepatoma was maintained in Buffalo female rats. A conjugate of the beta-subunit of CG and tetanus toxoid (CGb-tt) was used for immunization and induction of CG antibodies. An av of 1.30 ug of the immunogen was injected sc in the interscapular area on days 0, 7, and 14; after the last injection, 14 days were allowed for optimization of the antibody production before implantation of the respective tumor. One of two con control groups was administered purified tetanus toxoid, approx 0.7 ug/injection, following the same schedule as with CGb-tt, while the other received saline only. After sacrifice, serum was tested for anti-CG antibodies with the use of the hCG-beta-RIA kit. The two control groups did not show any binding of 125I-hCG, while all animals immunized against CG had a significant titer of CG antibodies. Induction of anti-CG antibodies induced a significant reduction of tumor mass in all preimmunized animals for both tumor models. Tumor take after implant of 10 mg Stadie slices, however, was not prevented by preimmunization. Histopathology and growth pattern of the tumors were identical in all groups. Results demonstrated that immunization against CG has a definitive biological effect in transplantable solid tumors by significantly retarding the growth of the two tumor models. (16 Refs)

75. EFFECTS OF DNA SYNTHESIS INHIBITORS ON THE INDUCTION OF HCG SUBUNITS AND ALKALINE PHOSPHATASE IN HELA S3 CELLS.

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Diss Abstr Int [B]; 42(11):4396-B 1982

The synthesis of human chorionic gonadotropin (hCG) alpha- and beta-subunits and alkaline phosphatase has been examined in HeLa S3 cultures. In general, compounds which influenced deoxynucleotide metabolism were good inducers of these ectopic proteins, while agents which altered DNA structure by intercalation or covalent binding were poor inducers. The greatest induction was achieved with sodium butyrate. Induction of ectopic products was synergistic (or at least additive) when intermediate inducers were added in combination with butyrate, suggesting different modes of action for these compounds. The simultaneous addition to cultures of various paired combinations of these intermediate inducers resulted in no greater induction than that observed with either drug alone, indicating similar or competing mechanisms among them. Addition of RNA or protein synthesis inhibitors to cell culture medium containing sodium butyrate, aphidicolin, or phosphonoformic acid abruptly ceased the production of hCG-alpha subunit indicating RNA and protein synthesis were both required for induction of this protein. (no Refs)

76. ENHANCED AND REVERSED GROWTH IN VIVO OF A PREGNANCY-DEPENDENT MOUSE MAMMARY TUMOR (TPDMT-4) BY A GONADOTROPIN-RELEASING HORMONE AGONIST ANALOG.

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Eur J Cancer Clin Oncol; 18(5):495-505 1982

TPDMT-4 pregnancy-dependent mammary tumors grow continuously in DDD female mice carrying pituitary isografts (PI) ectopically or bearing an sc 17beta-estradiol plus progesterone (EP) pellet. A gonadotropin-releasing hormone (GnRH) agonist (D-leucyl6, des-glycyl-NH210, prolyl-ethylamide9) GnRH (TAP-144), was examined for its antitumor activity in these experimental systems. TAP-144 was injected ip at doses of 300 and 600 ug 6x weekly, when tumors grew to significant sizes. TAP-144 enhanced tumor growth during the first 2 weeks and subsequently reversed it in a dose-related manner in PI-bearing mice. The agonist did not affect tumor growth in the absence of ovaries in these mice. In ovariectomized mice, TAP-144 enhanced EP pellet-induced tumor growth but never reversed it. In ovariectomized, PI-bearing mice. TAP-144 first enhanced and subsequently reversed tumor regrowth induced by ovarian grafts to a greater extent when commencing it simultaneously with ovarian grafting than 30 days before it. The agonist also exerted the dual effects on TPDMT-4V ovarian-dependent subline tumors in the absence of PI. In TAP-144-treated mice, enhanced tumor growth was related to many solid corpora lutea in ovaries and fully developed mammary glands, but reversed growth was related to atrophied luteal components and mammary glands. The results suggest that TAP-144 enhances tumor growth first via its stimulative action on the pituitary-ovarian axis and causes tumor regression later via its direct inhibitory action on ovaries. (Author abstract) (31 Refs)

77. EFFECT OF CRYOSURGERY OF PROSTATE IN SERUM GONADOTROPIN LEVELS IN PROSTATIC CANCER.

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Cryobiology; 19(3):237-241 1982

Pituitary gland response to releasing hormone using the LH-RH loading test before and 4 wk after cryosurgery of the prostate was investigated in eight patients with advanced prostatic carcinoma. In pre- and postoperative comparisons of all patients, there were no significant differences detected before and after surgery. But pituitary response to the releasing hormone was compared before and after the surgery in each of the patients; in one, depression and facilitation of FSH and LH secretion, respectively, were observed and there was a variation in the response of gonadotropin in each patient. Although the number of observable patients is still too low to draw any definite conclusions from the test results, one possible interpretation is that cryosurgery of the prostate may influence hormonal secretion from the pituitary gland. (Author abstract) (19 Refs)

78. MEDICINAL THERAPY OF PITUITARY TUMORS.

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Dtsch Med Wochenschr; 107(23):883-886 1982

The current status of medicinal therapy of pituitary tumors is discussed. Preadenomatous hyperprolactinemia and prolactinoma may be treated with bromocriptine (BC). BC can produce a reduction in size of the tumor as well as a reduction in serum levels of prolactin. If the tumor does not respond to BC, surgery may be required. BC can be used for prevention of recurrences of prolactinoma. For the treatment of growth hormone- or ACTH-producing tumors or of hormonally inactive tumors, BC has not been shown to be sufficiently effective to replace surgery. (17 Refs) (In GER)

79. AROMATASE IN THE CENTRAL NERVOUS SYSTEM.

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Cancer Res; 42(8,Suppl):3274s-3276s 1982

Central (central nervous system and pituitary) aromatization appears to be a fundamental process for endocrine control and development. Metabolism of androgens to estrogens and the subsequent metabolism of estrogens have been proven in many species, including humans, and linked to estrogen action. Thus, aromatization appears to initiate or to be involved in activities of importance to endocrine function at the central level and their effects peripherally. In the context of breast cancer, central aromatization relates to the control of gonadotrophins and other pituitary-brain hormones which may effect metabolism at the level of the breast. For example, follicle-stimulating hormone can increase aromatization and may be a factor in the control of such metabolism in breast tissue. (Author abstract) (27 Refs)

80. RHABDOMYOSARCOMA-INDUCED HYPERCALCEMIA IN A NUDE MOUSE.

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Cancer; 50(1):94-96 1982

Hypercalcemia in nude mice with a rhabdomyosarcoma transplanted from a hypercalcemic patient is reported. The tumor had been transplanted to nude mice from a 15-yr-old girl with hypercalcemia which appeared as the rhabdomyosarcoma developed and metastasized to the peritoneal and pleural cavities. The tumor was successfully transplanted to nude mice, which presented an elevated serum calcium level. No remarkable elevation of serum parathyroid hormone or 1alpha,25-dihydroxyvitamin D was found in the mouse with rhabdomyosarcoma. Injection of indomethacin restored the elevated serum calcium level to the normal range. The prostaglandin E2 level was approx 15 x higher in the tumor-bearing mouse serum than in the control mouse serum. These data indicate that hypercalcemia in this patient can be ascribed to prostaglandin E2 produced by the rhabdomyosarcoma. (Author abstract) (18 Refs)

RECEPTOR/ BINDING SITES

81. PROLACTIN RECEPTORS IN CULTURED RAT MAMMARY TUMOR CELLS. UNMASKING OF CELL SURFACE RECEPTORS BY ENERGY DEPLETION.

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J Biol Chem; 257(12):6971-6977 1982

The level of specific binding of 125I-labeled ovine prolactin to primary cultures of 7,12-dimethylbenzanthracene-induced rat mammary tumors can be increased 2-to 20-fold by a variety of chemically distinct respiratory inhibitors or uncouplers of oxidative phosphorylation. Independent of the type of inhibitor used, binding increases when the cellular ATP level is decreased by at least 70%. This change is due to an apparent increase in the number of binding sites. Receptor affinity (Kd = 4 x 10(-10) M) is not affected. The binding of 125I-labeled epidermal growth factor to tumor cells is not similarly altered. Primary cultures of normal mammary gland from perphenazine-stimulated rats and tumor tissue slices also show increased prolactin binding in the presence of these inhibitors. In contrast, binding to slices from lactating mammary gland, liver, ovary, adrenal gland, or kidney is unaffected. The low level of prolactin binding in untreated tumor cell cultures is not due to hormone degradation or rapid down-regulation of receptors. Electron microscope autoradiography indicates that in the presence of 2,4-dinitrophenol prolactin binding is limited to the cell surface. Sites that can be activated by energy depletion are also localized on the cell surface. Thus, prolactin receptors in proliferating normal and neoplastic rat mammary tissue exist in two forms on the cell surface, an active form that recognizes and binds prolactin and an inactive form that does not. When cellular ATP levels are normal, the inactive form predominates (2 to 20 inactive sites for each active site). When ATP levels are markedly decreased, receptors are converted to the active (binding) form. In target cells where prolactin is not trophic, inactive receptors are absent or energy depletion does not activate the binding sites. This pool of cryptic cell surface receptors may enable certain prolactin target tissues with the ability to rapidly change their level of available prolactin receptors and thus regulate their hormonal response. (Author abstract) (60 Refs)

82. THYROTROPIN RELEASING HORMONE RECEPTORS IN REGULATION OF PROLACTIN GENE EXPRESSION IN GH CELLS.

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Biochem Biophys Res Commun; 106(3):811-817 1982

The thyrotropin releasing hormone (TRH) receptor-modulated regulation of prolactin (PRL) gene expression was studied in three GH cell strains (rat pituitary tumor cells in culture). The three strains synthesize different amounts of PRL and exhibit different responses to TRH. Binding affinities and the number of receptors/cell were studied and the effect of epidermal growth factor on PRL gene expression in the different cell strains was explored. One strain (GH4C1) responded to TRH by stimulating PRL production while the hybrid strain (928-9b) and the bromodeoxyuridine-resistant strain (F1BGH12C1) did not. When binding of 3H-TRH was studied as a function of TRH concentration, the affinities of TRH to its specific receptors were similar in both GH4C1 and 928-9b cells. However, the number of TRH receptors/cell was significantly different in the two strains; GH4C1 cells had a max number of specific binding sites of 1.05 x 10(5)/cell, while 928-9b cells had a max number of 0.16 x 10(5)/cell. Thus, in the two strains, the TRH-responsive GH4C1 cells and the TRH-nonresponsive cells, the total number of TRH binding sites per cell was much less in the TRH-nonresponsive cell line. The inadequate number of TRH receptors in 928-9b cells may be responsible for the nonresponsive property of the hybrid cells to TRH and a possible role of the number of specific receptors in the regulation of the peptide hormone action is suggested. (11 Refs)

83. INSULIN PROMOTES THE GROWTH OF F9 EMBRYONAL CARCINOMA CELLS APPARENTLY BY ACTING THROUGH ITS OWN RECEPTOR.

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Biochem Biophys Res Commun; 106(3):974-980 1982

Antibody directed against the insulin receptor (anti R) was used to investigate whether insulin acts through its own receptor to promote growth of F9 embryonal carcinoma cells. Proliferation of F9 cells was enhanced by the addition of anti R to the serum-free growth medium, with a max response at 30 ug/ml anti R. Thus, occupancy of the insulin receptor stimulated F9 cell growth. In the absence of mitogen, F9 cells exhibited a low level of growth; high concentrations of control IgG enhanced the basal growth of these cells. The binding properties of the F9 insulin receptor were characterized. At equilibrium 50% of the 125I-insulin tracer was effectively displaced by 10 nanog/ml of unlabeled insulin. Some competition for 125I-insulin binding to F9 cells was exhibited by greater than 500 nanog/ml of specific cell receptors for multiplication-stimulating activity (MSA) and proinsulin. With 25 ug/ml proinsulin, half max displacement of 125I-insulin occurred, while 2 ug/ml MSA produced only a 35% decrease in 125I-insulin binding. Scatchard analysis demonstrated heterogeneity or negative cooperativity between insulin receptors. Preincubation with anti R for 30 min specifically blocked 125I-insulin binding, but not binding of 125I-MSA. With 40 ug/ml anti R, 125I-insulin binding decreased 50%. Control IgG did not displace insulin tracer. Thus, anti R probably exerts its growth-promoting effect by acting through the insulin receptor. (18 Refs)

84. REGULATION OF INSULIN RECEPTORS IN ERYTHROID CELLS.

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Metabolism; 31(7):728-732 1982

The effect of exogenous insulin on receptor concentration and affinity of cells of the erythroid series was studied using murine Friend erythroleukema (FEL) cells and rabbit reticulocytes. Undifferentiated and differentiated FEL cells, models for erythroblasts and normoblasts, conducted both active protein synthesis and messenger RNA synthesis; reticulocytes were incapable of mRNA synthesis, but were able to synthesize protein, and mature erythrocytes could synthesize neither. Each type of cell was placed into Temin's medium containing 15% fetal calf serum with or without 10 nanoM insulin for 18 hr at 37 C. Decreased binding of (125-I)-iodoinsulin tracer following insulin exposure by erythroblasts, normoblasts, and reticulocytes was due to changed receptor concentrations. Insulin treatment did not significantly alter receptor affinity characteristics for any cell type except the erythrocyte. Basal values for receptor concentration were 30,000 sites/cell for erythroblast, 10,000 sites/cell for normoblast, 190 sites/cell for reticulocyte, and 45 sites/cell for erythrocyte. The ability to 'down-regulate' was lost as follows: erythroblasts down-regulated by 60%, normoblasts by 43%, and reticulocytes by 30%; erythrocytes did not down-regulate. These results are consistent with the hypothesis that protein synthesis is needed for insulin receptor down-regulation. The possibility that mature erythrocytes cannot reduce insulin receptor concentration in response to hyperinsulinemia suggests that utilizing erythrocytes as models of total body receptor concentrations may only apply to chronic changes. (29 Refs)

85. TROPHOBLASTIC CELLS OF THE HYDATIDIFORM MOLE CONTAIN A B1-SUBTYPE ADRENERGIC RECEPTOR.

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J Clin Endocrinol Metab; 55(2):341-346 1982

Both beta-1 and beta2-adrenergic receptors have been previously described in normal human placental homogenates; the cells upon whose surface membranes these receptors reside have not been identified. In order to show that a beta1-adrenergic receptor is present on trophoblastic cells, the cells which mediate maternal-fetal transport and produce placental hormones, beta-adrenergic receptors were demonstrated in membrane fractions of human hydatidiform mole. Microscopic sections of the mole samples used demonstrated edematous villi lined by trophoblastic cells with minimal nontrophoblastic (stromal or vascular) contamination compared with placenta. (-)-[3H]Dihydroalprenolol [(-)-[3H]DHA]binding to molar membranes was reversible and saturable to a single class of sites (Kd = 0.97 +-0.12 nM; n = 7; maximum binding capacity, 72.9 +-6.4 fmol/mg protein). (-)-[3H]DHA binding was associated with catecholamine-stimulated adenylate cyclase activity. Agonist competition for the molar beta-adrenergic receptor showed the order of potency to be (-)isoproterenol much greater than norepinephrine = epinephrine, characteristic of a beta1-adrenergic receptor subtype. Competition for (-)-[3H]DHA binding to trophoblastic membranes by the beta-adrenergic receptor subtype-specific agents metoprolol (beta1 selective) and zinterol (beta2 selective) was also characteristic of a homogenous subtype of beta1-adrenergic receptors. Because beta1-adrenergic receptors alone were seen on trophoblast cells, the beta2-adrenergic receptor in placenta must reside on nontrophoblastic elements (stromal or vascular endothelium). No differences in beta-adrenergic receptor binding were seen related with ploidy (2 or 3 N), the presence or absence of a fetus, or the progression of the mole to choriocarcinoma. Two choriocarcinoma cell lines, BeWo and JEG-3, however, showed no specific (-)-[3H]DHA binding. Human trophoblast contains beta1-adrenergic receptors coupled to catecholamine-sensitive adenylate cyclase, supporting a role for catecholamines in the regulation of placental metabolism. (Author abstract) (26 Refs)

OTHER RELATED STUDIES

86. RETINOIDS INCREASE TRANSGLUTAMINASE ACTIVITY AND INHIBIT ORNITHINE DECARBOXYLASE ACTIVITY IN CHINESE HAMSTER OVARY CELLS AND IN MELANOMA CELLS STIMULATED TO DIFFERENTIATE.

Scott KF, Meyskens FL, Russell DH
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Proc Natl Acad Sci USA; 79(13):4093-4097 1982

Transglutaminase (TGase; R-glutaminyl-peptide:amine gamma-glutamyltransferase, EC 2.3.2.13) and ornithine decarboxylase (ODCase; L-ornithine carboxy-lyase, EC 4.1.1.17) activities were measured after the addition of retinoid analogs to Chinese hamster ovary (CHO) cells released from quiescence and Cloudman S91 (CCL 53.1) mouse melanoma cells stimulated to differentiate with alpha-melanocyte-stimulating hormone (MSH, melanotropin). In both cell culture lines, we detected a biphasic increase in TGase activity and a single peak of ODCase activity within 7 hr after release or stimulation. Retinoid analogs altered the expression of the initial TGase peak in both CHO and melanoma cells. Retinol increased the activity of TGase 1 hr after release in CHO cells, and the activity remained elevated until hr 4. A broad peak of TGase activity also occurred after the addition of alpha-difluoromethylornithne, an irreversible inhibitor of ODC-ase, and after addition of alpha-difluoromethylornithine plus retinol. In mouse melanoma cells, retinoic acid plus MSH markedly enhanced the activity of the initial TGase peak compared to MSH alone. Retinoic acid alone also increased TGase activity biphasically in these cells without the addition of MSH. These studies suggest that retinoid effects that increase TGase activity may alter the ODCase expression in proliferation and differentiation. (Author abstract) (36 Refs)

87. DOES THE ECTOPIC SECRETION OF ACTH EXIST?.

Vereshchagina GV
Res. Inst. Biological Testing of Chemical Compounds, Kupavna, USSR
Eksp Onkol; 4(3):11-19 1982

Incidence of various hormonal disorders in cancer patients is reviewed, with special emphasis on the ectopic production of ACTH. The criteria of ectopic ACTH syndrome include correlation between increased blood level of ACTH and growth of tumor; absence of direct involvement of adrenals or hypothalamo-pituitary region; presence of ACTH in the tumor tissue; arterio-venous gradient of ACTH concentration; ability of tumor cells to produce ACTH in vitro; changes in functional state of ACTH-secreting endocrine glands; and persistence of elevated ACTH concentration following removal of ACTH-secreting endocrine glands. (91 Refs) (In RUS)

88. GASTRIN PROTECTION AGAINST CHEMICALLY INDUCED GASTRIC ADENOCARCINOMAS IN WISTAR RATS: HISTOPATHOLOGY OF THE GLANDULAR STOMACH AND INCIDENCE OF GASTRIC ADENOCARCINOMA.

Tatsuta M, Yamamura H, Taniguchi H, Tamura H
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JNCI; 69(1):59-66 1982

The effects of gastrin on the histopathology of the glandular stomach and on the incidence of gastric carcinoma induced by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were investigated in inbred Wistar (W) rats. Prolonged administration of gastrin after treatment with MNNG significantly reduced the incidence of adenocarcinomas of the glandular stomach. In addition, atypical glandular proliferations were significantly less frequent and were smaller, and the incidence of marked mucosal atrophy was significantly reduced in both the antral and oxyntic gland mucosae. Both atypical glandular hyperplasia and mucosal atrophy are precursors of gastric cancers; prolonged administration of gastrin to rats after treatment with MNNG suppressed development of precursors of gastric cancer and so prevented development of gastric cancers. (Author abstract) (19 Refs)

89. S-100-LIKE IMMUNOREACTIVITY IN NEUROENDOCRINE TUMORS (MEETING ABSTRACT).

Ulich TR, Yang K, Wen DR, Cochran AJ, Lewin KJ
Division of Surgical Pathology, University of California, Los Angeles, CA, 90024
Gastroenterology; 82(5,part2):1200 1982

S-100 is an apparently unique marker for neural crest derived cells such as glial cells, Schwann cells, and melanocyte-derived cells. In view of the possible neural crest origin of carcinoid tumors, 15 formaldehyde-fixed, paraffin-embedded neuroendocrine tumors (11 gastrointestinal carcinoids, 2 pulmonary carcinoids, and 2 medullary carcinomas) were studied by the PAP technique with an antiserum to S-100. Eight tumors contained scattered cells that showed focal cytoplasmic immunoreactivity of variable intensity. Immunoreactivity was seen in a minority cell population of the tumor. Immunoreactivity was present in three types of tumor cells: Uniform polygonal cells within the center of tumor nests, columnar cells palisaded at the periphery of tumor nests, and dendritic cells within and around the periphery of tumor nests. These findings raise the possibility that S-100-like immunoreactivity is the expression of a neural crest histogenesis of carcinoid tumors. The histogenesis of neuroendocrine cells and tumors has been the subject of much controversy. These findings could also be explained by immunologic cross-reactivity between S-100 and a known or unknown neuroendocrine polypeptide hormone. (no Refs)

90. PHEOCHROMOCYTOMA AND CARDIOVASCULAR SYSTEM.

Kalinin AP, Davydova IV
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Ter Arkh; 54(5):143-148 1982

Literature data on the involvement of cardiovascular system in the patients with pheochromocytoma are reviewed. Cardiovascular disorders in pheochromocytoma patients are associated with arterial hypertension as well as with direct effect of catecholamines on the blood vessels and the heart. Catecholamines stimulate alpha and beta adrenergic receptors, enhance glycemia and lipolysis, and induce arrhythmia. Morphological manifestations of cardiovascular disorders in catecholamine-producing tumors include mild atherosclerosis of coronary and cerebral arteries, hypertrophy and necrosis of papillary muscle, swelling and proliferation of the endothelium of small arteries and arterioles, myocardial infarction, and syndrome of disseminated intravascular coagulation. Clinical manifestations of pheochromocytoma depend upon the relationship between epinephrine and norepinephrine levels in the blood and in the urine. Catecholamine myocardial dystrophy results in the decrease of myocardial contraction and insufficiency of the left ventricle. Treatment of cardiovascular complications consists of administration of adrenergic receptor blockaders. (89 Refs) (In RUS)

91. THYMIC ORIGIN OF THE PROLACTIN-DEPENDENT NB2 LYMPHOMA CELL LINE.

Fleming WH, Pettigrew NM, Matusik RJ, Friesen HG
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Cancer Res; 42(8):3138-3141 1982

Blast cells in acute leukemia and lymphoma appear to be 'frozen' at various stages of lymphoid cell differentiation. The enzymatic and antigenic phenotypes expressed by these cells often correspond to the gene products of their normal precursors. We have used various immunocytochemical and enzymatic techniques to identify membrane, nuclear, and cytoplasmic markers associated with prolactin-dependent Nb2 lymphoma cell line. The Nb2 cells, whether stationary or in log-phase growth, did not express any surface immunoglobulin. However, 100% of the Nb2 cells bound both a monoclonal antibody raised to rat thymocyte W3/25-HLK, which specifically binds an antigenic determinant on rat T-helper cells, and second monoclonal antibody OX8-HL, which identifies rat nonhelper T-cells. Transmission electron microscopy showed no evidence of phagocytic vacuoles, and activity of the lysosomal enzyme muramidase was also absent. There was no evidence of the DNA polymerase enzyme terminal deoxynucleotidyl transferase. Alpha-Naphthyl acetate esterase activity was indicated in about 50% of the Nb2 cells by a faint particulate cytoplasmic staining similar to that found in thymocytes. Rosette formation with guinea pig erythrocytes, a property of mature rat thymocytes, was not observed with Nb2 cells. The data suggest that the Nb2 tumor may have arisen naphthyl from a thymocyte at an intermediate stage of differentiation. The presence of Thy-like alpha-naphthyl acetate esterase pattern and the binding of both W3/25-HLK and OX8-HL support the thymic origin and relative immaturity of these lymphoid cells. It is becoming increasingly apparent that a significant proportion of lymphomas and leukemias also originate in undifferentiated thymic cells. (Author abstract) (15 Refs)

92. EFFECTS OF A PROLACTIN-SECRETING TUMOUR ON COPULATORY BEHAVIOUR IN MALE RATS.

Weber RF, Ooms MP, Vreeburg JT
Dept. Internal Medicine III, Univ. Hosp. Dijkzigt, Rotterdam, The Netherlands
J Endocrinol; 93(2):223-229 1982

The effect of the transplantable prolactin- and ACTH-secreting tumor 7315a on male copulatory behavior was investigated. Castrated tumor-bearing rats implanted with testosterone-filled capsules exhibited significantly longer latencies to first mount or intromission and to ejaculation than castrated control animals. In contrast to the number of intromissions, the number of mounts before ejaculation of the tumor-bearing rats was considerably increased. However, when castration was carried out in addition to adrenalectomy, the differences in copulatory behavior between tumor-bearing rats and control rats were no longer present. During the last tests for copulatory behavior the tumor-bearing rats had serum prolactin concentrations of more than 4,000 ng/ml while control rats had less than 100 ng/ml. Plasma testosterone levels produced by silicone elastomer capsules were neither affected by the presence of the tumor nor by adrenalectomy. It was concluded that hyperprolactinemia does not suppress the copulatory behavior of adrenalectomized rats. (Author abstract) (21 Refs)

93. LYMPHOKINES: A FORUM FOR IMMUNOREGULATORY CELL PRODUCTS.

Pick E, Landy M
Dept. Human Microbiology, Sackler Sch. Medicine, Tel-Aviv Univ, Ramat-Aviv, Tel-Aviv, Israel
Lymphokines 2: 313 pp., 1981.

Lymphokine (LK) activities are discussed. A systematic screening for LK activities detectable in the supernatants of continuous lymphoid and myeloid cell lines is presented. Present knowledge of T-cell growth factor (TCCF) and prospects for future LK studies stemming from the discovery and rapidly expanding application of TCCF are considered. Other topics discussed include the following: the central role played by T- and B-cell growth factors in the primary antibody response in vitro, the immune response in vitro, the role of antigen-specific T-cell factors in both help and suppression, the role of soluble factors in macrophage-T-cell interaction, the mechanism of action of LK, the mechanism of action of WBC migration inhibitory factor, the biological universality of LK, cytokine-like mediators secreted by malignant cells, tumor necrosis factor, the design of a method for enumerating LK-secreting cells, and the significance of the presence of LK in the tissues of animals and humans. (852 Refs)

94. HORMONES AND MENTAL CHANGES.

Lueg MC
Tulane Medical Center Hosp. and Clinic, 1415 Tulane Ave., New Orleans, LA, 70112
J La State Med Soc; 134(4):32-37 1982

Six case reports are presented to illustrate the fact that endocrine or metabolic disease may be a factor in patients who present with primary mental problems or functional illness. One patient with severe psychotic depression had Cushing's syndrome; a second with neuroses showed an elevated immunoreactive insulin level compatible with insulinoma. Pheochromocytoma may also be associated with neuropsychiatric manifestations. (7 Refs)

95. EFFECTS OF HEXAMETHYLENE BISACETAMIDE (HMBA), SODIUM BUTYRATE (BA) AND DIMETHYL SULFOXIDE (DMSO) ON ALPHA-FETOPROTEIN (AFP), ALBUMIN AND TRANSFERRIN PRODUCTION BY A HEPATOMA CELL LINE IN SERUM-FREE MEDIUM (MEETING ABSTRACT).

Hughes EH, Kim N
National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:145 1982

Low molecular weight compounds such as DMSO and BA are known to modulate the production of AFP, albumin and transferrin in hepatoma cell lines. In order to further study these effects of DMSO, BA as well as HMBA, growth of rat hepatoma cell line McA-RH 7777 (7777) was obtained on plates precoated with human fibronectin in a serum-free medium. Concentrations of AFP, albumin and transferrin were determined by radioimmunoassay. The medium consisted of 1:1 mixures of Ham's F-12 and Dulbecco's modified Eagles supplemented with insulin, iron saturated transferrin and selenium and 15 mM Hepes. The production of AFP, and transferrin was 200-350 and 15-30 ng/ 10(5) cells/24 hr, respectively. Albumin was nondetectable. Treatment with BA induced a dose-dependent increase in synthesis of AFP and transferrin whereas treatment with HMBA and DMSO caused a dose-dependent decrease in the synthesis of both AFP and transferrin. No induction of albumin synthesis was observed. Similar effects of all three agents on 7777 are observed after treatment with DMSO and BA in serum supplemented medium, except that albumin synthesis was induced 6-fold with BA and HMBA induced AFP synthesis 2-fold. The capacity of BA (4 mM) to induce albumin secretion and of HMBA (4 mM) to induce AFP secretion under serum containing growth conditions but not in defined medium may reflect an absence of permissive factor(s) in the defined medium. (1 Ref)

96. SIDE EFFECTS OF DRUGS. ANNUAL 6. A WORLDWIDE YEARLY SURVEY OF NEW DATA AND TRENDS.

Dukes MN, Elis J
Netherlands Commitee for the Evaluation of Medicines, Ministry of Health, Koopmanstraat 1, 2288 BC Rijswijk, The Netherlands
Side Eff Drugs Annu 6: 478 pp., 1982.

Current information relating to adverse drug reactions and interactions from the clinical point of view is presented. Drugs are classified according to primary field of application or for the properties for which they are most generally recognized. In borderline cases some supplementary discussion has been included relating to secondary fields of application. Fixed combinations of drugs are dealt with according to their most characteristic component. Agents covered include CNS stimulants and anorectic agents; antidepressants; lithium; social drugs; hypnotics; sedatives; anticonvulsants; opioid analgesics; narcotic antagonists; antipyretic analgesics; anti-inflammatory analgesics and drugs used in rheumatoid arthritis and gout; general anesthetics; therapeutic gases; local anesthetics; muscle relaxants; drugs affecting autonomic functions or the extrapyramidal system; drugs used on the skin; antihistamines; drugs used in bronchial asthma and cough; cardiac glycosides; drugs used in dysrhythmias; anti-anginal and beta-adrenoreceptor blocking drugs; drugs acting on the peripheral circulation; hypotensive drugs; diuretic drugs; metals; metal antagonists; antiseptic drugs and disinfectants; penicillins; cephalosporins; tetracyclines; other antibiotic drugs; antifungal drugs; antiprotozoal drugs; sulfonamides; miscellaneous antibacterial and antiviral drugs; drugs used in tuberculosis and leprosy; anthelminthic drugs; enzymes; enzyme inhibitors; immunologic preparations; blood and blood products; iv infusions (soln and emulsions); drugs affecting blood clotting, fibrinolysis, and hemostasis; gastrointestinal drugs; drugs used in the management of gallstones; vitamins; corticosteroids; corticotrophins; sex hormones and related compounds including oral contraceptives; thyroid and antithyroid drugs; insulin; glucagon; oral hypoglycemic drugs; miscellaneous hormones and prostaglandins; drugs affecting lipid metabolism; cytostatic and immunosuppressive drugs; radiologic contrast media; drugs used in ocular treatment; drugs used in non-orthodox medicine; and miscellaneous drugs. (3118 Refs)

97. HYPERPLASTIC AND NEOPLASTIC ERYTHROPROLIFERATIVE DISEASES INDUCED BY ONCOGENIC MURINE RETROVIRUSES.

Scolnick EM
Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20205
Biochim Biophys Acta; 651(4):273-283 1982

Structure of Harvey (HV) and Kirsten virus (KV), transforming protein of HV and KV, and Friend virus complex are discussed. Comparison of polycythemia- and anemia-inducing strains of spleen focus-forming virus (SFFV) is presented. Friend murine leukemia virus-induced (F-MuLV) disease and pathophysiology of F-MuLV-induced disease are described. Possible pathophysiological relationships between Friend virus-induced erythoproliferation and Harvey sarcoma virus (Ha-SV)-induced erythroleukemia are discussed. Biochemistry of transforming proteins of erythroleukemia viruses is reviewed. One possible advantage that studies of erythroleukemia have is that the abnormal proliferation of erythroid precursor cells induced by SFFV or Ha-SV is accompanied by a decreased requirement by these cells for erythropoietin. Studies on erythroid cells are limited by the availability of large quantities of purified erythropoietin. Both polycythemia-inducing SFFV and Ha-SV induce the abnormal proliferation of fully hemoglobinized erythroid colonies in cell culture colony assays for the viruses. Results might suggest that Ha-SV infection of stem cells could be a method for generating stem cell lines. (81 Refs)

98. DECREASE OF TUMOR GROWTH IN MICE AFTER INTRAVENOUS THYMOSIN-TREATED BONE MARROW CELL INJECTION.

Cupissol D, Rey A, Goldstein AL, Serrou B
Laboratoire d'Immunopharmacologie des Tumeurs, INSERM U 236, ERA-CNRS No. 844, Centre Paul Lamarque, Hopital Saint-Eloi, B P 5054, 34033 Montpellier Cedex, France
JNCI; 69(1):27-31 1982

The effect of iv injection in C57BL/6 mice of 3 x 10(7) bone marrow cells preincubated in either thymosin fraction V or thymosin alpha-1 was evaluated on the growth of a 3-methylcholanthrene-induced transplantable tumor in a syngeneic system. The effect was then compared to that elicited by theophylline or levamisole, which both demonstrated thymosin-like action in vitro. The results showed significantly retarded tumor growth (P less than 0.001) and prolonged survival time (P less than 0.001) when thymosin fraction V was used. The same results were obtained with thymosin alpha-1 with use of the same protocol but only one-twentieth of the concentration of fraction V. Theophyline and levamisole demonstrated no antitumor effect. (Author abstract) (42 Refs)

99. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.

Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
Isr J Med Sci; 18(4):433-438 1982

The possible association of oral contraceptives (OC) and menopausal estrogens (ME) on development of breast cancer is reviewed. The high incidence of breast cancer concurrent with extensive OC-ME usage, considered together with the relatively high hormone dependence of breast tumors and the placement of the breast as a target organ in the estrogen-progesterone hormonal pathways supports this association. Theories of the hormonal etiology involve estriol, progesterone, androgens, and the pineal gland; however, the specific hormonal etiology is unclear. Most studies have demonstrated significantly decreased risk of benign breast disease in women using OC. Since increased parity and early first birth are potentially protective conditions for breast cancer, OC, by simulating pregnancy, may exert a protective effect. The incidence of benign breast disease appears to be inversely related to the amount of progesterone in different OC. No significant overall increase in the risk of breast cancer has been demonstrated among users of OC. However, specific subgroups in which an increased risk was shown have been identified, including women with previous biopsy of benign breast disease. Evidence is available associating ME with an increased risk of endometrial carcinoma. Recent studies have demonstrated a positive association between ME and breast cancer. Caution is suggested in long-term use of OC and the continuous use of ME for periods greater than 10 yr should be reconsidered. (57 Refs)

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CHARACTERIZATION OF NON-STEROID HORMONES IN EXPERIMENTAL AND IN VITRO SYSTEMS

1. UNUSUAL FORMS OF BETA-LIPOTROPIN (BETA-LPH) OF MOUSE PITUITARY TUMOR ATT-20 CELLS (MEETING ABSTRACT).

Lee TH, Lee MS
Veterans Administration Medical Center and Albert Einstein College of, Medicine Bronx, NY, 10468
Fed Proc; 41(3):1181 1982

We incubated mouse pituitary tumor AtT-20 cells (ATCC CCL89) obtained from American Type Culture Collection in Ham F-10 medium at 37 C. After an extraction with 5 N acetic acid containing 1 mM each of methylphenylsulfonylfluoride and iodoacetamide, the labelled hormones were immunoprecipitated in a double antibody system using an antiserum specific to beta-LPH, and examined in sodium dodecylsulfate-acrylamide gel electrophoresis. We detected appreciable amounts of labelled hormones with apparent molecular weights of 45-50k and 70-75k in addition to the well characterized 30-35k ACTH-beta-LPH common precursor and its degradative products. In

HE 20.3173/2

short incubations (5 min or less) the 70-75k molecule was not detected; but in longer incubations (60 min), both 70-75k and 45-50k molecules were detected in appreciable amounts. When an antiserum to ACTH was used in the immunoprecipitation, comparable results were obtained. Since it has been well established by incorporation studies in intact cells and in cell-free translation of messenger RNA that the primary gene product of these hormones in normal pituitary cells of rats, mouse, and cattle as well as in mouse pituitary tumor cell lines is a 30-35k ACTH-beta-LPH common precursor, we tentatively conclude that the observed unusual forms may be products of post-translational modification and may serve as storage forms of these hormones. (no Refs)

2. CHARACTERIZATION OF GAMMA-MELANOTROPIN-LIKE IMMUNOREACTIVITY AND ITS SECRETION IN AN ADRENOCORTICOTROPIN-PRODUCING MOUSE PITUITARY TUMOR CELL LINE.

Oki S, Nakao K, Tanaka I, Kinoshita F, Nakai Y, Imura H
Second Div., Dept. Internal Medicine, Kyoto Univ. Faculty Medicine, 54 Shogoin Kawaharacho, Sakyo-ku, Kyoto, 606, Japan
Endocrinology; 111(2):418-424 1982

A putative hormone in the N-terminal region of the ACTH/beta-endorphin (beta-EP) precursor protein, gammaMSH, was studied by RIA with an antiserum against gamma3MSH in ACTH-producing mouse pituitary tumor cells, AtT-20/D16v. Serial dilution of the culture medium or the cell extract gave parallel lines to the standard curve on the RIA for gammaMSH. Rat median eminence extracts enhanced the release of gammaMSH-like immunoreactivity (gammaMSH-LI) concomitant with ACTH-like immunoreactivity (ACTH-LI) and beta-EP-like immunoreactivity (beta-EP-LI). Dexamethasone suppressed the release of gamma-MSH-LI as well as ACTH-LI and beta-EP-LI. Gel exclusion chromatography of the culture medium and the cell extract has revealed that gamma-MSH-LI consists of two peaks; one eluted near the elution position of beta-lipotropin and the other near the elution position of beta-EP. There was no peak corresponding to the elution position of synthetic gamma3MSH. However, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) has demonstrated that gammaMSH-LI migrated at five positions with mol wt of 31K, 21-23K, 16-17K, 13-14K, and 3.8K, respectively. The 31K gammaMSH coincided with the migration position of 31K ACTH or 31K beta-EP, and 21-23K gammaMSH coincided with the position of 21-23K ACTH on SDS-PAGE. The 16-17K gammaMSH coincided with the mouse 16K fragment (reported by Eipper and Mains) of ACTH-beta-lipotropin precursor protein in the migration in SDS-PAGE and in immunoreactivity to anti-gammaMSH antiserum. [3H]Glucosamine was incorporated into 16K, 13K, and 3.8K gammaMSH. These results suggest that AtT-20/D16v cells produce gammaMSH-LIs with mol wt of 31K, 21-23K, 16-17K, 13-14K, and 3.8K, and they are secreted concomitantly with ACTH-LI and beta-EP-LI. (Author abstract) (28 Refs)

3. PULMONARY CARCINOIDS: IMMUNOHISTOCHEMICAL DEMONSTRATION OF BRAIN-GUT PEPTIDES (MEETING ABSTRACT).

Yang K, Ulich T, Taylor I, Cheng L, Lewin K
Department of Surgical Pathology, University of California at Los Angeles Hospital, Los Angeles, CA
The Endocrine Lung in Health and Disease, June 2-4, 1982, Washington, D.C. The George Washington University Medical Center 31 pp., 1982.

The purpose of this study was to investigate the presence and distribution of neuroendocrine products within bronchial carcinoid tumors. Antisera raised against serotonin, gastrin, somatostastin, motilin, bombesin, calcitonin, secretin, glucagon, ACTH, neurotensin, and pancreatic polypeptide carboxyterminal hexapeptide were employed to immunohistochemically stain seven pulmonary carcinoids. Argentaffin and argyrophil stains were also performed on all cases. Serotonin-like immunoreactivity was present in four tumors, pancreatic polypeptide-like immunoreactivity in four tumors, bombesin-like immunoreactivity in two tumors, and ACTH-like immunoreactivity in one tumor. The cells shown to contain neuroendocrine products constituted a minority cell population in all tumors except the ACTH-immunoreactive tumor. Five tumors were argyrophilic, and one was argentaffinic. The non-neoplastic respiratory epithelium overlying one tumor contained bombesin-like immunoreactivity, but otherwise no immunoreactivity was noted in the respiratory mucosa. The patient whose tumor demonstrated ACTH-like immunoreactivity presented clinically with Cushing's syndrome, and his tumor contained a predominance of ACTH-secreting cells. This study suggests that pulmonary carcinoids, like their abdominal counterparts, contain a variety of neuroendocrine products and may produce more than one neuroendocrine product. Serotonin and pancreatic polypeptide-like immunoreactivity were the most prevalent neuroendocrine products demonstrable in the present study. (no Refs)

4. HORMONAL FACTORS IN THE INDUCTION OF LEYDIG CELL TUMORS IN MICE.

Healey PK

University of Health Sciences/The Chicago Medical School, Chicago, IL

Diss Abstr Int [B]; 42(10):3965-B 1982

Differences between serum LH (luteinizing hormone), FSH (follicle stimulating hormone) and PRL (prolactin) levels in Leydig Cell tumor (LCT)-sensitive male A/J and LCT-resistant B6/D mice treated with estrogens were examined. The role of ACTH in the development of LCT in cryptorchid male A/J mice was studied. Male mice of the A/J and B6/D strains were treated weekly with 20ug of estradiol benzoate (EB) in corn oil, or a one-time implant of a 10% DES (diethylstilbestrol)-cholesterol pellet starting at one month of age. Serum levels of LH in estrogen-treated animals were reduced to 1 ng/ml or less within two months, while levels in the control animals averaged over 2.5 ng/ml for the same time period. Serum FSH levels were reduced during estrogen administration, while serum PRL levels increased in DES-treated animals over control. Testes weights decreased in both strains during the first eight months of estrogen treatment, thereafter increasing in the A/J mice but not in the B6/D mice. While increases in testes weights correlated with gross tumor development. LC atrophy followed by hypertrophy and hyperplasia appeared often as early as three months of treatment. LCT development in estrogen-treated A/J mice occurred during a decline in serum LH and FSH levels, and an elevation in serum PRL levels. Surgically cryptorchid LCT-sensitive male A/J mice were treated weekly with 24U of ACTHAR in Gelatin, or a 10% DES-cholesterol pellet implant, or both ACTH and DES. Five out of eighteen ACTH-treated animals developed hyperplastic foci of abnormally-appearing Leydig Cells, while gel-treated controls were normal. Seventeen out of ninteen DES-treated animals developed hyperplastic foci of LC while cholesterol pellet controls foci of LC did not appear. All of thirty ACTH/DES-treated animals developed hyperplastic foci, while all control animals were normal. (no Refs)

5. BIOACTIVE AND IMMUNOREACTIVE ADRENOCORTICOTROPIN IN NORMAL EQUINE PITUITARY AND IN PITUITARY TUMORS OF HORSES WITH CUSHING'S DISEASE.

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Endocrinology; 111(2):559-563 1982

Equine Cushing's disease is caused by hypersecretion of ACTH by hyperplasia or adenomas of pars intermedia (PI) cells, in contrast to human Cushing's disease, which is caused by hyperplasia or adenomas of pars distalis (PD) ACTH-secreting cells. We assayed both bioactive and immunoreactive (IR) ACTH in two normal equine pituitary glands and in the PD, PI, and pars nervosa of four such glands, as well as in the PI adenomas of five horses with Cushing's disease. In normal horse pituitaries, as in those of other species, most of the bioactive and IR-ACTH was found in PD, much less in PI, and only traces in pars nervosa. In PI adenomas of horses with Cushing's disease, bioactive ACTH concentrations were similar to those in normal PI, but the total tumor content of bioactive ACTH exceeded that of normal whole pituitary. IR-ACTH concentrations were even higher in PI tumors, suggesting that some of the tumor ACTH was biologically inactive. Plasma IR-ACTH, which, like the PI adenoma tissue, presumably included a major fraction of bioactive ACTH, was greatly elevated in five horses with Cushing's disease and would account for the adrenal hyperplasia and hyperfunction observed in these animals. (Author abstract) (29 Refs)

6. CHARACTERIZATION OF HIGH MOLECULAR WEIGHT CALCITONIN- AND ACTH-IMMUNOREACTIVE PROTEINS PRODUCED BY SMALL CELL LUNG CANCER TUMOR CELLS (MEETING ABSTRACT).

Gropp C, Luster W, Havemann K
Department of Hematology and Oncology, University of Marburg, Marburg, W. Germany
The Endocrine Lung in Health and Disease, June 2-4, 1982, Washington, D.C. The George Washington University Medical Center 31 pp., 1982.

In sera of about 200 patients with lung cancer, the peptide hormones calcitonin, ACTH, beta-lipotropin, and beta-endorphin were determined by radioimmunoassay: 57% of the patients with small cell carcinoma and 10% of the patients with squamous cell carcinoma exhibited elevated calcitonin levels. ACTH and beta-endorphin were increased in 33% and 45%, respectively, of patients with small cell carcinoma. In order to investigate the biochemical nature of these peptides, high molecular weight polypeptide fractions obtained from sera, tumor tissues and media of long term cell cultures, were separated by gel chromatography. Three immunoreactive calcitonin proteins with molecular weights of 100,000, 50,000 and 20,000 were isolated from all three sources by gel filtration and polyacrylamide gel electrophoresis under non-denaturing conditions. Two of the high molecular weight calcitonin fractions were degraded to molecular weights of about 17,000 and 3,400 (molecular weight of monomeric calcitonin) by incubation with sodium dodecyl sulphate. Moreover, the calcitonin-immunoreactive proteins were characterized by their behavior in ion exchange chromatography. Two fractions, with the molecular weights of 50,000 and 20,000, bound to DEAE (diethylaminoethyl)-sephacel at neutral pH and low conductivity and eluted at slightly acid pH or in the presence of 55 nM NaCl. The fraction having a molecular weight of 100,000 did not bind to DEAE-sephacel. None of the three protein fractions exhibited any interaction with a cation exchange gel. Additionally, the fraction having a molecular weight of 100,000, in contrast to the other two polypeptides, is characterized by a high sensitivity to proteolytic enzymes. Gel filtrations of cell culture media resulted in big-ACTH-beta-lipotropin fractions with molecular weights of about 150,000, 30,000 and 20,000 and only a small amount of monomeric ACTH. In summary, the different lung tumors seem to synthesize a corticotropin-beta-lipotropin precursor molecule and/or a calcitonin prohormone. (no Refs)

7. THE CHARACTERIZATION OF ALPHA-SUBUNIT OF GLYCOPROTEIN HORMONE PRODUCED BY UNDIFFERENTIATED CARCINOMA.

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Endocrinol Jpn; 29(1):11-19 1982

The glycoprotein alpha-subunit (gp-a) of human chorionic gonadotropin (HCG) was isolated from the urine of a 32-yr-old woman patient with an undifferentiated, metastatic carcinoma of the femur that produced large amounts of gp-a. The gp-a was compared with gp-a from normal pregnant women. The carcinoma did not produce complete HCG molecules or HCG-beta subunits (HCG-b). The specific immunoactivity of gp-a was 0.92 (mg alpha-subunit/mg protein) after extraction by the kaolin-acetone method. Gp-a showed identical immunoantigenicity to that of standard gp-a in the homologous HCG-alpha radioimmunoassay. Disc electrophoresis demonstrated a mol wt of 18,000 daltons for tumor gp-a, while standard HCG consisted of two components with mol wt of 19,000 and 28,000 daltons. Tumor gp-a showed close similarity to standard gp-a in amino acid composition. Tumor gp-a contained slightly more aspartic acid, serine, glutamic acid, and glycine and slightly less half-cystine and methionine than standard gp-a. In isoelectric focusing tests, gp-a produced by the tumor or by normal pregnant women was distributed over the range pH 3.5-6.0, while standard gp-a was distributed over the range pH 6.0-8.0. Tumor gp-a did not combine in vitro with HCG-b. Results suggest that tumor gp-a is identical with standard gp-a in the protein moiety but has undergone intracellular modification of the carbohydrate moiety. This modification renders tumor gp-a incapable of combining with HCG-b. (20 Refs)

8. HUMAN CHORIONIC GONADOTROPIN: STRUCTURAL, BIOLOGIC, AND IMMUNOLOGIC ASPECTS.

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Semin Oncol; 9(2):163-173 1982

The chemical, biological, and immunological properties of human chorionic gonadotropin (HCG) are described. The glycoprotein nature of HCG, its primary structure, associated carbohydrate moieties, hormonal activity, its antigenic nature and the subsequent development of sensitive radioimmunoassays are among topics discussed. The development of such assay techniques has particular relevance in the clinical management of trophoblastic disease. (78 Refs)

9. HUMAN LUNG SMALL-CELL CARCINOMA: THE AMPHIBIAN PEPTIDE CONNECTION (MEETING ABSTRACT).

Lazarus LH, DiAugustine RP, Jahnke GD
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The Endocrine Lung in Health and Disease, June 2-4, 1982, Washington, D.C. The George Washington University Medical Center 31 pp., 1982.

Among the different histopathologic classes of human lung tumors, small cell carcinomas (SCC) are considered to produce the highest incidence of clinical ectopic endocrine disorders. Many of these endocrinopathies are caused by the release of peptide hormones from constituent cells of the tumor. The presence of cytoplasmic neurosecretory-type granules in some SCC cells indicates a morphological correlate with endocrine cells. Recently, immunoreactivity (ir) to the amphibian peptides bombesin and physalaemin was found in extracts of a human SCC passaged in athymic (nude) mice. In the present study, the physicochemical properties of SCC bombesin-ir and physalaemin-ir were compared with those of the corresponding known amphibian peptides by reverse-phase HPLC (high performance liquid chromatography) following selected chemical and enzymic modifications. In each case, the retention times of tumor-ir were identical to that of the synthetic peptide: (1) increased retention of bombesin-ir by a change in pH of the mobile phase from 2.3 to 7.0 was attributed to the loss of charge on His 12, thereby increasing hydrophobicity; (2) oxidation of a thiol-containing amino acid in both bombesin-ir and physalaemin-ir produced elution patterns which suggested the presence of Met; (3) removal of the NH2-terminal less than Glu of bombesin-ir by pyroglutamate aminopeptidase produce a more hydrophobic molecule; and (4) digestion of bombesin-ir by trypsin yielded a peptide fragment that eluted earlier than the standard peptide. The increased retention of this fragment at pH 7.0 suggests the presence of a His residue. In addition, the threshold dose of tumor physalaemin-ir (HPLC-purified) required to produce a contractile response in the isolated guinea-pig ileum was similar to that of the amphibian peptide. (no Refs)

CLINICAL, DIAGNOSTIC AND PROGNOSTIC STUDIES

10. ECTOPIC PRODUCTION OF ACTH BY WILMS' TUMOR.

Pombo M, Alvez F, Varela-Cives R, Iglesias-Diz JL, Martinon F, Castro-Gago M, Pena J
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Horm Res; 16(3):160-163 1982

The authors present the second documented case of Wilms' tumor associated with the ectopic ACTH syndrome. This is a 7 1/2-yr-old girl who, on examination at the time of admission, had the classical cushingoid appearance. A large hard mass was palpable in the right side of the abdomen. Hormonal assays were consistent with Cushing's syndrome; the serum ACTH levels were extremely high. After surgical removal of the mass, we suspected a Stage I Wilms' tumor; this was confirmed by histopathological studies. After surgery, the girl quickly lost her cushingoid appearance and weight excess. Postoperative serum ACTH levels were normal. Ectopic hormone syndromes associated with tumors in childhood are discussed as well as the possible mechanism involved in the ectopic production of ACTH. (Author abstract) (13 Refs)

11. CIRCULATING ANTI-ADRENOCORTICOTROPIN-ADRENOCORTICOTROPIN IMMUNE COMPLEXES IN PATIENTS WITH SMALL CELL CARCINOMA OF THE LUNG (MEETING ABSTRACT).

Havemann K, Gropp C, Luster W
Department of Hematology and Oncology, University of Marburg, Marburg, W. Germany
The Endocrine Lung in Health and Disease, June 2-4, 1982, Washington, D.C. The George Washington University Medical Center 31 pp., 1982.

It has been reported that patients with lung cancer, particularly of the small cell variety, are prone to secrete, ectopically, peptide hormones, some of which can cause paraneoplastic syndromes. Circulating immune complexes have been reported to be associated with small cell carcinoma. Both phenomena may play a role in the pathologic proliferation of this tumor. This present study was designed to investigate whether there is a correlation between these two findings. In sera of more than 190 patients with lung cancer of various histologic types, ACTH was determined by radioimmunoassay. In 35% of all cases with small cell carcinoma, elevated ACTH levels were found. In the sera of these patients, circulating immune complexes were isolated by affinity chromatography on protein A-sepharose. In order to demonstrate ACTH-anti ACTH immune complexes, the immune complexes bound to protein A-sepharose were eluated and chromatographed on immune affinity columns containing anti ACTH bound to sepharose. The results showed that an ACTH-immunoreactive IgG fraction was bound to these columns. Upon further investigation of sera from some patients without any demonstrable ACTH, free antibodies against ACTH were detected by titration in two radioimmunoassays. In patients who had elevated ACTH levels before therapy, after response to therapy, a decrease of measurable ACTH corresponding to an increase of free ACTH-antibodies was found. These results suggest that there is a relationship between the ectopic production of auto-immunoreactive ACTH by a tumor and the formation of circulating ACTH-IgG immune complexes. (no Refs)

12. ADRENAL TUMORS FROM AN INTERNIST'S VIEWPOINT.

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Roentgenpraxis; 35(7):268-272 1982

Clinical symptoms, biochemical diagnosis, and conservative therapy of adrenal tumors are reviewed. Diseases resulting from adrenal tumors include hypercortisolism (HC), hirsutism in females, Conn's syndrome (CS), pheochromocytoma (PC), and clinically occult tumors. HC is manifested early in the course of the disease as Cushing's syndrome. Functional changes include hypertension, muscular weakness, disturbance of sexual function, and diabetes. Diagnosis of HC requires a daily profile of the plasma cortisol level and measurement of urinary excretion of cortisol; other tests for HC include the ACTH and lysin-vasopressin tests. Therapy of choice is surgery; for conservative therapy, the adrenolytic agent mitotane-lysodrene may be used. Virilizing tumors are recognized by masculinization of hair growth in female patients; and tumors may be diagnosed by measurement of testosterone and dehydroepiandrosterone sulfate in the plasma. Therapy of choice for the virilizing tumors is surgery; inoperable tumors may be treated with the antiandrogen cyproterone acetate. Aldosterone-producing tumors cause CS, a nonspecific group of symptoms, and diagnosis is confirmed by measuring levels of aldosterone in the serum. Hyperaldosteronism may be treated with the aldosterone antagonist spironolactone, but this drug has serious side-effects. PC may be characterized by acute or chronic hypertension; PC patients may however, be normotensive. Conservative therapy consists of administration of the alpha-blocker phenoxybenzamine. Occult tumors do not present symptoms of hormonal imbalance, although in later stages they may cause Addison's disease. (16 Refs) (In GER)

13. EXCRETION OF 17-KETOSTEROIDS AND CATECHOLAMINES DURING COMPLEX TREATMENT OF BREAST CANCER PATIENTS.

Godovanets BI
Dept. Surgery, Medical Inst., Ivano-Frankovsk, USSR
Klin Khir; (5):60 1982

The effect of complex radical treatment on excretion of 17-ketosteroids (17-KS) and catecholamines was studied in 249 patients with breast cancer (BC). Prior to being treated, the BC patients showed a stage-dependent increase in 17-KS excretion, decrease in norepinephrine excretion, and increase in epinephrine excretion. Radical treatment brought about normalization of the epinephrine excretion. (no Refs) (In RUS)

14. DERANGEMENT OF CYCLIC NUCLEOTIDE SYSTEMS OF MONONUCLEAR BONE MARROW CELLS IN ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) (MEETING ABSTRACT).

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Pediatr Res; 16(4,part2):215A 1982

Concentrations of both adenosine 3':5' monophosphate (cAMP) and guanosine 3':5' monophosphate (cGMP) were determined during incubations of mononuclear cells isolated from marrows of ALL patients at diagnosis and at subsequent remission periods. Incubations for 1-20 min in the presence of 1-methyl-3-isobutyl-xanthine resulted in equal increases of both nucleotides whereas addition of sodium nitroprusside resulted in large elevations of cGMP only. Both isoproterenol and epinephrine increased markedly concentrations of cAMP in cells (greater than 70% lymphocytes) isolated from patients undergoing remission of ALL. Carbamylcholine addition resulted in slight increases of the cGMP concentration, whereas serotonin exhibited pronounced stimulatory effect upon guanylate cyclase activity. Cells isolated from ALL patients at diagnosis (greater than 90% blasts) exhibited diminished responsiveness of both cyclic nucleotides to hormonal stimuli, the catecholamine activation of adenylate cyclase being almost absent. The sensitivity had reappeared already by 2 weeks after the initiation chemotherapy. Attempts are made to correlate the characteristics of the cAMP and cGMP systems with the growth behavior of the cells in long-term cultures. The techniques may eventually be used to determine the effectiveness of particular therapeutical interventions in individual patients. (no Refs)

15. RADIOENZYMATIC DETERMINATION OF PLASMA L DOPA AND ITS METABOLITES IN NEUROBLASTOMA (MEETING ABSTRACT).

Alvarado CS, Faraj BA, Camp VM, Verras A, Kim TH, Ragab AH
Department of Pediatrics and Radiology, Emory University School of Medicine, Atlanta, GA
Pediatr Res; 16(4,part2):198A 1982

Neuroblastoma (NB) is a tumor of the neural crest characterized by abnormalities of tryosine metabolism. The purpose of this study was to evaluate plasma L-dopa and its respective metabolites-Dopamine, Norepinephrine and epinephrine in a group of patients with Neuroblastoma. Plasma L-Dopa and its metabolites were measured by a radioenzymatic technic in 12 children with NB and in 12 other children with different malignancies (control group). The average values for Plasma L-Dopa, Dopamine and norepinephrine were 44.8 ng/ml, 420.4 Pg/ml and 1404 Pg/ml respectively in children with NB, as compared to 1.67 ng/ml, 36.6 Pg/ml, and 227 Pg/ml for the control group. Urinary catecholamines were measured in 24 hour urine samples in 10 patients and they were elevated in only 6 patients. However, plasma L-Dopa, Dopamine and Norepinephrine were significantly elevated in 11 of the 12 children with NB. Follow-up determinations of L-Dopa and its metabolites correlated with the clinical course of the patients. Measurement of Plasma L-Dopa, Dopamine and Norepinephrine by this technic is a sensitive marker for the diagnosis and follow-up of children with Neuroblastoma and appears to be more accurate and less cumbersome than measurement of urinary catecholamines. (no Refs)

16. EXTRA-ADRENAL PHEOCHROMOCYTOMA.

Zang M, Liu G
Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Zhonghua Miniao Waike Zazhi; 3(1):72-74 1982

Among 47 cases of pheochromocytoma (PCC) confirmed at surgery and by pathological examination, an unusually large number (19, 40.4%) were found outside the adrenal cortex. Biochemical testing showed that in 11/13 cases with extra-adrenal PCC, urinary norepinephrine was greater than 300 ug/24 hr. With the use of post-peritoneal air contrast and renal vein nephrography, the accuracy of the diagnosis of extra-adrenal PCC was low, only 5/13. Recent application of 'B' ultrasonography and computer tomography is of great assistance in the diagnosis of extra-adrenal PCC, although care must be exercised when the tumor is small. Among the 19 patients, 4 tumors could not be removed surgically because of adhesion to other organs; 1 patient died from excessive blood loss during surgery. Among the 19 tumors, 7 were malignant. Six of seven malignant tumors had metastases, while the remaining tumor had infiltrated adjacent organs. These findings suggest that extra-adrenal pheochromocytomas tend to be malignant. (16 Refs) (In CHI)

17. PINEAL REGION TUMORS: ENDOCRINOLOGICAL ASPECTS.

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Childs Brain; 9(3/4):267-273 1982

Relationships between pineal tumors and diabetes insipidus, precocious puberty, neuro-ophthalmologic signs, and other diagnostic indicators are discussed. Evidence supporting the view that the pineal gland and the superior cervical ganglia constitute an integration center for hormonal and neural signals includes production of two antigonadal principles in response to environment, feedback control of pineal activity by reproductive hormones, the role of norepinephrine released from pineal nerve endings in pineal metabolism, and the role of substances other than sex steroids in modifying pineal function. Study of the hormonal effects strictly dependent upon pineal function is hampered by the lack of confirmed cases and the problem of correlating endocrine signs and neuro-ophthalmological abnormalities with histopathologic abnormalities. Diabetes insipidus is an important early clinical sign of pineal region tumors. It is important to distinguish diabetes insipidus of central origin (CID) from nephrogenic diabetes insipidus and psychogenic polydipsia. Both differential diagnoses can be made by tests involving vasopressin levels. Data of polyuria and/or polydipsia should never be underestimated, especially in the male child. Not only diabetes mellitus should be excluded, but CID as well; once a diagnosis of CID is established and the rare familial form excluded, a tumor of the pineal region should be considered. In the presence of CID a thorough and global endocrinological evaluation should be done to demonstrate adenopituitary deficiency, one of the early clinical signs of pineal region tumors. (13 Refs)

18. ENDOCRINE-ACTIVE TUMORS OF THE DUODENUM (APUDOMAS): A COOPERATIVE STUDY.

Woodtli W, Gemsenjager E, Heitz PU, Gloor F, Rosch W, Bosseckert H, Deyhle P
Bodenacherstrasse 14, 8121 Benglen, Switzerland
Praxis; 71(25):1045-1053 1982

Tumors of the duodenum (APUDomas) are reported in eight patients (6 men, 2 women; 35-67 yr old); five of the patients had tumors that showed endocrine activity (EA). The tumors included three solitary gastrinomas, one multiple gastrinoma with multiple endocrine adenomatosis (MEA), one carcinoid with G- and EC-cells, two argyrophilic APUDomas (1 PP-cell tumor and one unclassifiable tumor), and one undifferentiated APUDoma of the papilla of Vater. The solitary and multiple gastrinomas were associated with Zollinger-Ellison (ZE) syndrome. In the patient with MEA, several gastrinomas were detected by endoscopic biopsy. The patient with the carcinoid showed possible ZE syndrome, but since no preoperative tests were conducted, the syndrome could not be confirmed. Biopsy tissues from this patient showed metastases in 3/4 tumors; tumor growth, however, was slow. The argyrophilic APUDomas and the undifferentiated APUDoma showed no EA. Local symptoms included pain associated with the carcinoid, duodenal obstruction associated with the nonclassifiable argyrophilic APUDoma, and cholestasis associated with the APUDoma of the papilla of Vater. No local symptoms were associated with the gastrinomas. (14 Refs) (In GER)

19. PERCUTANEOUS TRANSHEPATIC VENOUS SAMPLING OF GASTRIN: VALUE IN SPORADIC AND FAMILIAL ISLET-CELL TUMORS AND G-CELL HYPERFUNCTION.

Glowniak JV, Shapiro B, Vinik AI, Glaser B, Thompson NW, Cho KJ
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N Engl J Med; 307(5):293-297 1982

The value of transhepatic venous sampling was assessed in eight patients (6 women, 2 men; 23-59 yr old) by attempting to identify the origin of gastrin hypersecretion. Five patients had multiple endocrine neoplasia type I, two had single sporadic gastrinomas, and one had G-cell hyperfunction. In all cases studied, gastrin responses to secretin were abnormal; one patient had a borderline elevated response, but was subsequently shown to have G-cell hyperfunction. Patients with multiple endocrine neoplasia type I differed in the site of maximal gastrin concentration; two patients had high levels in veins draining the head of the pancreas, one exhibited diffuse hypergastrinemia, and various other locations were indicated in three others. Patients with solitary tumors differed in the locations of highest gastrin concentrations. In multiple endocrine neoplasia type I, transhepatic venous sampling is generally unhelpful in treatment because of the multiple sites of origin of gastrin hypersecretion. In sporadic tumors the technique may indicate that the tumor is localized, and may allow cure by surgical excision. In the patient with G-cell hypersecretion, transhepatic venous sampling localized hypersecretion to the antrum, suggesting appropriate surgery. (18 Refs)

20. ENDOCRINE TUMORS OF THE PANCREAS.

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Ned Tijdschr Geneeskd; 126(17):766-771 1982

The pathogenesis of endocrine pancreatic tumors, the significance of the amine precursor uptake and of decarboxylated cells, the symptoms and therapy of such tumors are reviewed. These tumors include insulinoma, gastrinoma, Verner-Morrison syndrome, glucagonoma, somatostatinoma, pancreatic polypeptide-producing tumor, and carcinoids of the pancreas. Verner-Morrison syndrome may be due to the production of vasoactive intestinal polypeptide, pancreatic polypeptide, prostaglandins, or unknown hormones. Curative resection or, if impossible, alleviation of the symptoms of excessive hormone production are indicated in the treatment of endocrine pancreatic tumors. (52 Refs) (In DUT)

21. THE ACUTE EFFECT OF INTRAARTERIAL INFUSION OF STREPTOZOTOCIN IN HUMAN MALIGNANT ENDOCRINE TUMOURS OF THE GASTROINTESTINAL TRACT.

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Excerpta Med Int Congr Ser; 575:155-160 1982

The acute effect of intraarterial infusion of streptozotocin (STO) was studied in 10 patients (5 men, 5 women, mean age 65 yr) with endocrine tumors of the gastrointestinal tract. Seven patients had a pancreatic tumor (6 of the tumors produced more than one hormone), on a mid-gut tumor producing serotonin, and two a fore-gut tumor with gastrin production. All patients had liver metastases diagnosed by computed tomography, ultrasound, or angiography. STO, 2 g were infused at a rate 0.1 g/min. Tumors producing gastrin, pancreatic polypeptide (PP), and neurotensin showed a release of the hormone into circulation 40-60 min after start of STO infusion. A second peak of PP was noted 3-4 hr after administration. The hormone levels gradually diminished during the first months. Human chorionic gonadotropin (HCG) levels slowly increased in the circulation during the first day after treatment. Tumors and metastases were usually highly vascularized with newly formed tumor vessels. Dilatation of the arteries peripheral to the site of STO infusion were observed in 5/7 patients. Four of the patients had tumors producing vasoactive substances. In the intervals (4-6 wk) between infusions, plasma levels of vasoactive intestinal peptide (VIP), gastrin, and neurotensin decreased while those of PP and HCG subunits remained unchanged. Tumors producing VIP, insulin, and gastrin appeared to be most sensitive to therapy. (8 Refs)

22. IMPROVEMENT OF THE EFFICACY OF POSTOPERATIVE CHEMOTHERAPY IN LUNG CANCER PATIENTS.

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Dept. Thoracic Tumors, Res. Roentgenoradiological and Oncological Inst., Kiev, USSR
Klin Khir; (5):45-48 1962

Literature data on the efficacy of postoperative chemotherapy in lung cancer patients are reviewed. Experimental and clinical data indicated that administration of anticoagulants, glucose, insulin, or dimethyl sulfoxide reduced the toxicity of antineoplastic agents and enhanced their antitumor activity. (61 Refs) (In RUS)

23. CARCINOMAS OF THE CERVIX AND CORPUS UTERI IN HUMANS: STAGE-DEPENDENT BLOOD LEVELS OF SUBSTANCE(S) IMMUNOLOGICALLY CROSS-REACTIVE WITH INSULIN.

Pavelic K, Bolanca M, Vecek N, Pavelic J, Marotti T, Vuk-Pavlovic S (c/o Vuk-Pavlovic), Inst. Immunology, Rockefellerova 2, 41000 Zagreb, Croatia, Yugoslavia
JNCI; 68(6):891-894 1982

Inasmuch as the elevated levels of substance(s) immunologically cross-reactive with insulin (SICRI) in a diabetic woman with carcinoma of the corpus uteri decreased following the surgical removal of the uterus and ovaries 80 women with cervical carcinomas of various stages and 70 women with carcinomas of the corpus uteri of various stages were screened for the levels of SICRI and C-peptide. The levels of SICRI in the 2nd, 3rd, and 4th stages of the cancers were elevated (up to 6x above the normal levels of immunoreactive insulin) and stage-dependent. The levels of C-peptide, which are related to the insulin-secreting activity of pancreatic beta-cells, were normal and independent of the stage of cancer. (Author abstract) (19 Refs)

24. RADIOLOGICAL STUDY OF INFANTILE SELLA TURCICA IN MICROADENOMAS DIAGNOSIS.

Malena S, Fileni A, Barbuti D, Fariello G, Gugliantini P
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Childs Brain; 9(3/4):156-164 1982

Radiological alterations in children who were examined for suspected hypophyseal microadenoma are discussed, with reference to the value of traditional radiographic methods and computerized tomography (CT). A study of 30 patients between the ages of 4 and 15 with hypophyseal dysfunction revealed the following major single radiographic findings: posterior depression, reclined dorsum, double contour, asymmetrical dorsum, enlarged aditus, and increased sella. CT findings after contrast medium showed a nodular area of increased density in 56.7% of cases. Hormonal alterations were evident in many of the 14 patients from the series who were operated upon. Elevation or depression of gonadotropin and growth hormone and elevation of prolactin were observed, accompanied by such clinical findings as precocious puberty, hyposomia, polyuria-polydipsia, and dwarfism. In the presence of specific clinical evidence, the finding of even minimal radiographic alterations must be considered sufficient evidence of suspected hypophyseal pathology, justifying the immediate use of CT. Patients with initially negative radiographic and CT findings, but who continue to exhibit clinical signs of hypophyseal disorder, should be checked successively with plain radiograph only, to minimize radiation exposure and costs to the patient. (11 Refs)

25. NONMETASTATIC AND LOW-RISK METASTATIC GESTATIONAL TROPHOBLASTIC NEOPLASMS.

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Semin Oncol; 9(2):191-197 1982

Management of nonmetastatic and low-risk metastatic gestational trophoblastic neoplasia (GTN) is discussed. About 15% of patients develop nonmetastatic GTN following molar removal. Hemorrhage due to trophoblastic uterine perforation is a serious complication. Single agent chemotherapy is the treatment of choice, and methotrexate (MTX) and citrovorum factor (CF) is the preferred regimen. If a patient with nonmetastatic GTN no longer wishes to preserve fertility, hysterectomy plus adjuvant chemotherapy may be recommended. patients with nonmetastatic GTN are advised not to become pregnant until 12 mo of normal human chorionic gonadotropin levels have been achieved. Trophoblastic tumors metastasize in about 5% of patients following molar removal and infrequently after other gestational events. Sequential single agent chemotherapy with MTX-CF and actinomycin D has induced complete remission in 79/95 patients with low risk metastatic GTN. The remaining 16 patients achieved complete remission with combination chemotherapy with or without local resection. Protocols for the management of resistant disease are described. Surgical therapy plays a limited role in the management of low-risk metastatic GTN. (17 Refs)

26. NATURE OF INVASIVE MOLE AND ITS RATIONAL MANAGEMENT.

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Semin Oncol; 9(2):181-186 1982

The pathobiology, diagnosis and treatment of invasive mole are discussed. Invasive mole is usually diagnosed by persistent positive titer of human chorionic gonadotropin HCG and clinical symptoms after hydatidiform mole. Chemotherapy has provided excellent remission without surgery. Hysterectomy not only removes the reproductive potential, but still leaves the possibility of developing new metastases. Heterotransplantation of invasive mole and choriocarcinoma in nu/nu mice indicated no tumorigenicity or capacity for serial transplantation in the first, and potential for both in the latter. About 80% of well monitored patients treated solely by uterine evacuation exhibit a benign, self-limited hydatidiform mole. Invasive mole is a continuum of disease after hydatidiform mole, as indicated by urinary HCG patterns. Invasive mole is considered to be present at the time of evacuation of hydatidiform mole and remains as a persisting trophoblastic disease after hydatidiform mole. An immunologic mechanism is involved in the growth and invasiveness of the trophoblast. An immune selection mechanism may determine the outcome of the conceptus into spontaneous abortion or hydatidiform mole. Dynamic change in the production of blocking antibody may play an important role in the immune selection mechanism. Definitions and classification, incidence and diagnosis of invasive mole, and indications for and methods of treatment are also discussed. (26 Refs)

27. CHORIOCARCINOMATOUS CHANGE WITH IMMUNOCYTOCHEMICALLY HCG-POSITIVE CELLS IN THE GASTRIC CARCINOMA OF THE MALES.

Mori H, Soeda O, Kamano T, Tsunekawa K, Ueda N, Yoshida A, Fukunishi R
Dept. Pathology, Osaka Univ. Sch. Medicine, Kitaku, Osaka 530, Japan
Virchows Arch [Pathol Anat]; 396(2):141-153 1982

Gastric choriocarcinoma is a rare tumor and attracts interest because of its controversial pathogenesis. The present study reports a choriocarcinomatous change with immunocytochemically hCG-positive cells in the gastric carcinoma. The patients were males, one was 41 yr old and the other 42 yr old. The tumor of both cases consists of adenocarcinoma and choriocarcinoma. A sequential process of morphological transition of the adenocarcinoma to the choriocarcinoma can be traced. Indirect immunoperoxidase stain (PAP method) for human chorionic gonadotropin (hCG) demonstrates the localization of hCG in the syncytiotrophoblasts. Small number of cytotrophoblasts are weakly positive. None of the components of adenocarcinoma of both cases is positive for hCG. Human placental lactogen is not demonstrated in both cases. Stain for pregnancy specific beta-1 glycoprotein is weakly positive in the adenocarcinoma of one case but not in the choriocarcinoma. In one case, the concentration of hCG was 19.9 mIU/ml in the preoperative serum and decreased to 1.2 mIU/ml after gastrectomy. HCG production by gastric carcinoma was discussed with regard to possible pathogenesis of gastric choriocarcinoma. (Author abstract) (23 Refs)

28. DIFFICULT CASES OF TROPHOBLASTIC DISEASE AND ITS CLASSIFICATION AND MANAGEMENT.

Kim SJ
Dept. Obstretrics Gynecology, Kangnam St. Mary's Hosp., 505 Banpo-Dong, Kangnam-Ku, Seoul, Korea
Semin Oncol; 9(2):234-238 1982

Cases proving abnormally difficult in the diagnosis, classification, and management of trophoblastic disease are reported. These cases included a patient with hydatidiform mole with uncontrollable vaginal bleeding after mole evacuation. She was treated by dilatation and curettage, but a severe headache and coma developed. This patient died several hr later. In one case of hydatidiform mole, brain hemorrhage without evidence of lung metastases developed 3 wk after mole removal, and the patient achieved remission following craniotomy. Another case involved multiple metastases to almost all vital organs, including brain, liver, spleen and kidney. Other cases illustrated problems associated with recurrent mole, partial mole, hydatidiform mole in women aged over 50 yr, trophoblastic or molar embolism before and during molar removal, high human chorionic gonadotropin titer, huge molar pregnancy, invasive mole localized in intramesosalpinx, choriocarcinoma with term pregnancy, bone metastasis to femur, lung metastasis 13 yr after molar removal, brain metastasis with vital organ involvement, and initial and adjuvant surgery in drug-resistant patients. (7 Refs)

29. HYDATIDIFORM MOLE AND GESTATIONAL TROPHOBLASTIC DISEASE IN SOUTHERN CONNECTICUT.

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Dept. Obstetrics and Gynecology, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 06510
Obstet Gynecol; 59(1):78-84 1982

Of 127 patients with hydatidiform mole in southern Connecticut, 34 (28%) received chemotherapy for persistently elevated human chorionic gonadotropin (hCG) titers. An hCG regression curve was found to be useful if not mandatory for following patients. Excess uterine size, theca lutein cysts, uterine bleeding, and histologic trophoblastic hyperplasia were relative discriminators of the need for chemotherapy. In the absence of metastases, an hCG titer was the only valid discriminator for initiating chemotherapy, provided the patient could be followed consistently and reliably. The indications for initiating chemotherapy are discussed. Early diagnosis and close follow-up were associated with low morbidity. Five of six patients with metastatic disease were referred from outside the center. (Author abstract) (23 Refs)

30. TAMOXIFEN, AMINOGLUTETHIMIDE AND DANAZOL: EFFECT OF THERAPY ON HORMONES IN POST-MENOPAUSAL PATIENTS WITH BREAST CANCER.

Coombes RC, Powles TJ, Rees LH, Ratcliffe WA, Nash AG, Henk M, Ford HT, Gazet JC, Neville AM
Ludwig Inst. Cancer Res. (London Branch), Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England
Br J Cancer; 46(1):30-34 1982

Gonadotrophins, estradiol, androstenedione, testosterone and dehydroepiandrosterone sulfate (DHAS) were measured sequentially in 72 patients with advanced breast cancer receiving endocrine therapy of various types. Tamoxifen significantly reduced gonadotrophins but did not effect other hormones. Danazol also reduced gonadotrophins. Aminoglutethimide (AGT) reduced estradiol and DHAS but had no effect on gonadotrophins. The effects of administering tamoxifen, AGT and danazol together (TAD) were therefore examined. This combination reduced gonadotrophins, estradiol and DHAS, but no further than tamoxifen and AGT alone. The degree and duration of hormone suppression were similar in both responders and non-responders to tamoxifen, AGT or TAD, though patients responding to AGT showed more complete suppression at the end of the course of treatment, perhaps because they were treated longer. On relapse, adequate gonadotrophin and steroid suppression was demonstrated in patients receiving tamoxifen and AGT, respectively. We conclude that (a) response to endocrine therapy is unlikely to be related to the degree of endocrine suppression produced by the therapy; (b) combination endocrine therapy does not further reduce serum-hormone concentrations and (c) relapse is unlikely to be due to escape from the hormone-inhibitory effects of endocrine agents. (Author abstract) (11 Refs)

31. HUMAN CHORIONIC GONADOTROPIN-LIKE SUBSTANCE(HCG-LS)-PRODUCING UROTHELIAL CARCINOMA: IMMUNOHISTOLOGICAL LOCATION OF HCG-LS.

Kitajima K, Satoh Y, Okada K, Kishimoto T
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Jpn J Clin Oncol; 12(1):49-56 1982

Location of hCG-LS in tumor cells was investigated with the aid of immunohistochemical methods in three cases of hCG-LS-producing urothelial carcinoma tumors. The tumors revealed high levels of luteinizing hormone (LH) in the urine, serum, and tissues of the patients. Pathologically, two of the tumors were Grade III transitional cell carcinoma and one was undifferentiated carcinoma. The tumor tissues, obtained by surgery or autopsy, were fixed, embedded in paraffin, cut into 4 microns sections, and stained by an indirect immunoperoxidase technique using anti-hCG-beta serum (anti-HCGbs) to detect the hCG-LS. In Case 1, the substance reactive with the anti-HCGbs was found in the cytoplasm but not in the nucleus of undifferentiated carcinoma cells originating in the kidney. Many of the hCG-LS containing cells were large and pleomorphic, and some were similar to syncytiotrophoblastic cells. In Case 2, granular positive-staining was found in the cytoplasm but not in the nucleus of the anaplastic giant cells. In Case 3, the stained hCG-LS was found in none of the cancerous cells which, arranged in a papillary fashion, were obviously indicative of transitional cell carcinoma. The labeled material was located in the cytoplasm of anaplastic giant and trophoblastic-like cells. No specific location for the labeled material was revealed using controlled staining of specimens from all cases by the absorption test. Routine measurement of urinary and serum hCG-LS was suggested in patients with or suspected of having malignant tumors of the urinary tract. (15 Refs)

32. INVASIVE MOLE.

Lurain JR, Brewer JI
(c/o Brewer) Trophoblastic Disease Center, Northwestern Univ. Cancer Center, 303 East Chicago Ave., Chicago, IL, 60611
Semin Oncol; 9(2):174-180 1982

The pathobiology and treatment of invasive mole are discussed. Invasive mole is a benign disease, both clinically and pathologically. Three distinct clinical-pathological forms are recognized: (1) hydatidiform mole, (2) invasive mole or chorioadenoma destruens, and (3) choriocarcinoma. Diagnosis is made based on rising or persistent elevations of human chorionic gonadotropin (HCG) levels. Chemotherapy is very effective, and surgical procedures are unwarranted. Biopsy of metastatic vaginal lesion to diagnose trophoblastic disease is rarely justified. Chest x-rays, radionuclide liver-spleen scans, iv pyelograms and liver function tests are performed to screen for metastases when a diagnosis of persistent trophoblastic disease is made. The diagnosis of choriocarcinoma associated with hydatidiform mole requires histopathologic confirmation. Clinical evidence with HCG indicates that in 40% of patients with hydatidiform mole, invasive mole is present to some extent, but that most of these will undergo spontaneous regression. Clinical manifestations of the disease are discussed. All patients with invasive mole, metastatic or nonmetastatic, are considered to be at low-risk and are treated with methotrexate or actinomycin-D in sequence or alternately. Complete remission is diagnosed only after 3 consecutive wk of normal HCG titers. (27 Refs)

33. BETA-SUBUNIT HCG AND THE CONTROL OF TROPHOBLASTIC DISEASE.

Zarate A, MacGregor C
Dept. Endocrinology, Ap. Postal 99-073, Mexico DF
Semin Oncol; 9(2):187-190 1982

The usefulness of human chorionic gonadotropin (HCG) as a marker in trophoblastic disease is discussed. The Vaitukaitis method (or variations) for assaying HCG levels has been used to diagnose and monitor the response to treatment of women with gestational trophoblastic neoplasms. The success of chemotherapy can be accurately measured by measuring HCG levels, and for post-mole cases, two or three courses of therapy is curative, after beta-HCG has become undetectable. More than 90% of hydatidiform moles undergo spontaneous and complete remission during the 6 wk following removal, and this process can be followed by serial estimations of beta subunit. It is rare for trophoblastic growth to occur after beta-subunit of HCG has fallen spontaneously to undetectable levels. Beta-subunit HCG levels are consistently lower than HCG levels in all patients with trophoblastic disease, and frequent beta-subunit determinations should be performed during treatment until levels fall within the range of maximum sensitivity of the assay. The duration of follow-up after mole removal is 2 yr. The risk of becoming pregnant is minimal in patients whose beta-subunit levels have dropped to normal for at least 12 mo. (6 Refs)

34. GESTATIONAL TROPHOBLASTIC DISEASE IN HONG KONG.

Ma HK, Wong LC
Dept. Obstetrics Gynecology, Queen Mary Hosp., Hong Kong, Hong Kong
Semin Oncol; 9(2):224-233 1982

Past and current management of trophoblastic disease in Hong Kong is discussed. In 255 patients with moles, three types of regression pattern were observed. The most common type (71.3%) was that of continuous fall of human chorionic gonadotropin (HCG) level. In 75.3% of these patients, urinary HCG would return to the luteinizing hormone range and beta-HCG was not detected in serum within 2 mo. In five patients it required more than 3 mo for HCG levels to return to normal. In 22.8% of the patients in this series, the regression was slow. In a small group of patients (5.9%), there was a transient fall of HCG level after termination of the molar pregnancy, but the HCG level subsequently rose. By selecting postmolar patients with an unsatisfactory HCG regression pattern for methotrexate treatment, the incidence of choriocarcinoma was reduced. Methods of termination of molar pregnancy, prophylactic chemotherapy, pretreatment evaluation, dilatation and curettage, arteriography, detection of cerebral metastases, chemotherapeutic treatment modalities, duration of therapy, and the role of surgery are among other topics discussed. (25 Refs)

35. NEW CHEMOTHERAPEUTIC AGENTS IN THE MANAGEMENT OF GESTATIONAL TROPHOBLASTIC DISEASE.

Newlands ES
Dept. Medical Oncology, Charing Cross Hosp., Fulham Palace Road, London W6 8RF, England
Semin Oncol; 9(2):239-243 1982

Techniques of systemic chemotherapy used against gestational trophoblastic neoplasia at Charing Cross Hospital are discussed. In patients becoming resistant to methotrexate (MTX), the only active agents were found to be actinomycin-D and 6-azauridine. A combined response and improvement rate of 62% was observed in 24 drug-resistant patients treated with vincristine (VCR), MTX, and cis-platinum. All of these patients had previously extensive therapy using VCR and MTX in the multidrug CHAMOMA regimen. Some patients who have received the protocol containing cis-platinum have now been off treatment and in complete remission for up to 37 mo. In view of the side effects from cis-platinum, however, this treatment is limited to those who have become resistant to all other cytotoxic therapy. VP 16-213, a well tolerated drug with clear-cut activity in drug-resistant disease, has been successfully used as an initial chemotherapy, followed by a cycling sequence of drug therapy. Twenty-three of 23 patients resistant to other drugs have experienced reduction in human chorionic gonadotropin levels following VP 16-213. The integration of VP 16-213 and possibly also cis-platinum early in chemotherapy for selected patients may contribute to the cure of some cases who would otherwise become drug resistant. (16 Refs)

36. GROWTH IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (MEETING ABSTRACT).

Schedewie HK, Berry DH, Land V, Luft C, Sexauer L, Dickinson MJ, Elders MJ
Pediatric Department, University of Arkansas for Medical Sciences, Little Rock, AR
Pediatr Res; 16(4,part2):214A 1982

Increasing numbers of children surviving after treatment of acute lymphoblastic leukemia (ALL) have drawn attention to questions of long-term morbidity, including disease- or treatment- related growth retardation, Southwest Oncology Group project number 7581 was initiated in 12/1975 to evaluate the effect of ALL as well as chemotherapy and irradiation on body growth, serum growth hormone (GH) and somatomedin (Sm) concentrations. The study included 127 children from 5 participating institutions, 83 males and 44 females, with a mean age at ALL diagnosis of 6.6 years. Height, weight, and hormonal concentrations were determined at the time of initial diagnosis and at regular intervals for up to 5 years of follow-up. Eighty-four percent of children were observed for longer than 12 months. Boys less than 4 years showed significant growth retardation at diagnosis. Growth retardation persisted through ALL therapy so that 83% of these patients were growing below the 50th percentile by the end of observation. Linear regression analysis of growth rates in children with ALL versus normal standards confirmed differences in growth patterns. Serum GH and Sm concentration were similar to controls. However, hormone levels at initial diagnosis were significantly higher than during remission. In conclusion, our data suggest that a significant number of children with ALL are shorter than their peers prior to onset of therapy. GH and Sm levels appear to be elevated at the time of disease onset and to decrease with therapy. (no Refs)

37. SERUM PROLACTIN CONCENTRATION DURING TREATMENT OF CARCINOMA OF THE PROSTATE AND STIMULATION WITH SULPIRIDE (MEETING ABSTRACT).

Hantelmann W, Rost A, Hasselmann J
Urologische Klinik im Klinikum Steglitz der FU Berlin, Hindenburgdamm 30, Berlin, W. Germany
28 Tagung der Nordrhein-Westfalischen Gesellschaft fur Urologie, May 6-8, 1982, Krefeld, W Germany Nordrhein-Westfalischen Gesellschaft fur Urologie; 1982

Since estrogen-induced hyperprolactinemia should promote the development of hormone-refractory carcinomas of the prostate, the goal of this study was to determine the behavior of prolactin levels during treatment of carcinoma of the prostate with estrogen and cyproterone acetate as well as its ability to be stimulated before and during the above-stated therapy by means of sulpiride. In a randomized study 15 patients with histologically confirmed carcinoma of the prostate diagnosed for the first time were investigated. All of the patients had a stage tumor 3, nodes x, metastasis o malignancy. In addition to documentation of the clinical course plasma levels of prolactin, cyproterone acetate and estradiol were determined, both prolactin levels after sulpiride stimulation in the pretherapy phase and 6 mo after institution of the above stated therapy. During treatment with estradiol undecylate prolactin levels rose to upper normal values with an av of 19.0 ug/liter. Similar results were found during oral administration of cyproterone acetate with an increase to 24.6 ug/l. The smallest increase was recorded in the group with im administration of cyproterone acetate (11.0 ug/liter). Serum cyproterone acetate levels were higher by a factor of 10 when im administration 300 mg/wk was compared to oral administration (200 mg/day). Accordingly the easily elevated serum prolactin level during oral cyproterone acetate therapy must be checked against the clinical follow-up to see whether a reduction in the dose of cyproterone acetate to 100 mg/day is justifiable. (no Refs) (In GER)

38. HORMONES AND MEDICATIONS (MEETING ABSTRACT).

Lipsett MB
National Institutes of Health, Bethesda, MD, 20205
American Cancer Society National Conference: The Primary Care Physician and Cancer, June 24-26, 1982, Washington, DC American Cancer Society; :A7 1982

Hormones have been shown experimentally to act as cocarcinogens or promoters, ie, they facilitate the carcinogenic event. In the cases of breast and endometrium, those hormones that facilitate growth may also favor carcinogenesis in the human. There is good epidemiologic evidence of breast and endometrial cancer, the risk increasing with increasing duration of use. Periodic progestin-induced withdrawal will probably mitigate the risk of endometrial cancer after the menopause. Prolactin is the important promoter of mammary cancer in the rat and mouse, but its significance in women is still under study. Intermittently elevated prolactin levels have been noted in some women who subsequently developed breast cancer, but epidemologic studies of women who have received prolactin-releasing drugs such as reserpine and perphenazine have not disclosed increased risk. Diethylstilbestrol is listed as a carcinogen but any estrogen can induce mammary cancer in the rodent or vaginal adenosis in the neonatal mouse (an experimental model of human vaginal adenocarcinoma). (no Refs)

39. DETERMINATION OF HUMAN PROLACTIN AND ITS PRELIMINARY CLINICAL APPLICATION.

Kuang A, Ding T, Chen J, Xu M, Zhang D, Zhang M, Jin J, Chen s, Fan H, Cai W, Fang V
Shanghai Inst. Endocrinology, Shanghai, People's Republic of China
Zhonghua Neike Zazhi; 20(10):614-618 1981

Prolactin levels vary in different diseases and are important in the diagnosis of certain tumors such as microadenoma of the pituitary glands. In a preliminary study serum prolactin levels were found to be useful in the diagnosis of hypothyroidism, Cushing's syndrome and tumors of the pituitary and adrenal glands. Serum prolactin levels were generally normal in the other diseases studied. (10 Refs) (In CHI)

40. SPARSELY GRANULATED PROLACTIN CELL ADENOMAS OF THE PITUITARY GLAND. CORRELATION OF ULTRASTRUCTURE WITH PLASMA HORMONE LEVEL.

Dingemans KP, Assies J, Jansen N, Diegenbach PC
Dept. Pathology, Univ. Amsterdam, Wilhelmina Gasthuis, Eerste Helmersstraat 104, NL-1054 EG Amsterdam, The Netherlands
Virchows Arch [Pathol Anat]; 396(2):167-186 1982

The possible relationship between the preoperative plasma prolactin levels of patients having a sparsely granulated prolactin cell adenoma of the pituitary gland and the morphology of the tumors was studied by means of quantitative electron microscopy. To this end, a number of ultrastructural variables were chosen which are generally regarded to be indicative of cellular activity and which could be determined in a quantitative or semiquantitative way. These variables were determined in 19 adenomas from 17 patients and plotted against the corresponding prolactin levels. It appeared that marked endocrine activity was associated with a small number of granules per cell, a high frequency of exocytosis, and a marked development of the rough endoplasmic reticulum. Granule size and development of Golgi apparatus and lysosomes were not at all, or only poorly correlated with the plasma hormone levels. Finally, the number of mitochondria per cell showed a totally unexpected inverse correlation with endocrine activity. Due to the close mutual correlation existing between several of the variables investigated, combining them in a multivariate analysis did not significantly improve the correlation with the hormone level. (Author abstract) (49 Refs)

41. PROLACTIN: PHYSIOLOGY, PHARMACOLOGY, AND CLINICAL FINDINGS.

Fluckiger E, Del Pozo E, Von Werder K
Pharmaceutical Div., Preclinical Res., Sandoz Ltd., Basel, Switzerland
Monogr Endocrinol 23: 218 pp., 1982.

The physiology and pharmacology of prolactin in mammals, particularly man, are reviewed as an aid to the clinician and endocrinologists outside the clinic. Section 1 describes the synthesis, fate, and actions of prolactin. Molecular structure, secretion, storage, and the effects of prolactin on various organs and biological processes are presented. Section 2 describes mechanisms that regulate the secretion of prolactin. Drugs affecting secretion are discussed. Section 3 describes the physiology and pharmacology of human lactation, including hormonal mechanisms, the suckling reflex, lactational infertility, and inhibition of lactation. Section 4 describes hyperprolactinemia that is not related to tumors. Various clinical tests, effects of drugs, clinical syndromes, and therapy are discussed. Section 5 reviews pituitary prolactinomas. Topics discussed include pathophysiology of prolactinomas, secretion of hormones, clinical syndromes, the incidence of various syndromes, and hyperprolactinemia in the male. Therapeutic measures, including medical treatment, surgery, radiotherapy, and use of antiproliferative drugs are described. Management of prolactinomas and treatment of local tumor complications during pregnancy are discussed. (1530 Refs)

42. BROMOCRIPTINE TREATMENT OF PROLACTINOMAS AND PRIMARY HYPERPROLACTINEMIA.

Fossati P, Grenier J, Stevenard C, Fermon C, Christiaens J, Linquette M
Service d'Endocrinologie et Diabetologie, C.H.R. de Lille, rue du Professeur-Laguesse, F 59037 Lille, France
Ann Med Interne (Paris); 133(1):45-47 1982

The results of bromocriptine treatment are reported for 27 patients with macroadenomas, 16 patients with suspected adenomas, and 5 patients with primary hyperprolactinemia and a normal sella turcica. Prolactin levels were normalized in 43/48 cases, tumor regression was visualized once with computed tomography (CT) and reconstruction of the sella turcica was visualized twice with CT. (17 Refs) (In FRE)

43. EFFECTS OF TAMOXIFEN ON THE SERUM LEVELS OF OESTROGENS AND ADRENOCORTICAL STEROIDS IN POSTMENOPAUSAL BREAST CANCER PATIENTS.

Wilking N, Carlstrom K, Skoldefors H, Theve NO, Wallgren A
Dept. Surgery II, Sabbatsberg Hosp., S-11382 Stockholm, Sweden
Acta Chir Scand; 148(4):345-349 1982

Peripheral serum levels of cortisol, dehydroepiandrosterone (DHA), dehydroepiandrosterone sulfate (DHA-s), estradiol-17beta and total estrone were measured in 17 postmenopausal breast cancer patients and in age-matched healthy controls. In the breast cancer patients analyses were performed before and after 1, 2, 4, 8 and 12 wk of treatment with tamoxifen. Basal DHA levels were significantly higher in breast cancer patients than in controls; otherwise no significant differences were noted. Treatment with tamoxifen resulted in significantly elevated levels of cortisol throughout the period of treatment; this effect was probably solely due to an increase in transcortin levels. A transient but significant elevation in total estrone, probably related to liver function, was observed after 1 wk of treatment. No significant effects of tamoxifen were noted on serum DHA, DHA-s or estradiol-17beta. The results indicate that tamoxifen does not affect the adrenocortical steroid biosynthesis in postmenopausal women. The estrogenic effects of tamoxifen upon FSH, prolactin and the estrogen induced Pregnancy Zone Protein (PZP) in postmenopausal women, described in a previous communication from this group, are probably not due to any increase in the serum estrogens since this increase is transient and hardly impressive. The weak estrogenic effects of the tamoxifen-receptor complex itself may thus be sufficient to produce net estrogenic effects in subjects with low endogenous estrogens such as postmenopausal women. (Author abstract) (36 Refs)

44. INFLUENCE OF PREGNANCIES ON PROLACTINOMAS.

Rjosk HK, Fahlbusch R, Von Werder K
I. Frauenklinik der Universitat, Maistrasse 11, 8000 Munchen 2, W. Germany
Acta Endocrinol (Copenh); 100(3):337-346 1982

Hyperprolactinemic patients desiring pregnancy with a normal sella turcica or radiological evidence for a microprolactinoma without suprasellar extension were treated with bromocriptine. Females desiring pregnancy with large adenomas or suprasellar extension were treated by transsphenoidal surgery and in most instances post-operatively with bromocriptine. This differentiated management allowed the outcome of 65 pregnancies with delivery at term without complications related to the sella turcica. Considerable variations of prolactin levels during pregnancy suggesting different estrogen sensitivity of the prolactinoma cells were encountered. However, a rapid fall of the prolactin levels in 60 patients after termination of pregnancy indicated that estrogen stimulation does not cause persisting growth of the adenoma. In contrast, in 10% of pregnancies of hyperprolactinemic patients a reduction of the prolactin levels has been observed leading to spontaneous ovulatory cycles in five patients. (Author abstract) (22 Refs)

45. THE SERUM LEVELS OF TESTOSTERONE AND PROLACTIN IN PATIENTS WITH PROSTATIC CARCINOMA TREATED WITH VARIOUS DOSES OF FOSTROLIN AND BROMOCRIPTIN.

Jeromin L
Dept. Urology, Inst. Surgery, Medical Acad., Lodz, Poland
Int Urol Nephrol; 14(1):51-56 1982

Forty-five patients with histologically proven prostatic carcinoma were treated with a combination of fostrolin (diethylstilbestrol diphosphate) and bromocriptine at various dose levels. High doses of fostrolin produced a rise in prolactin levels and serum testosterone levels. The optimal dose of fostrolin was 3 g total initial therapy delivered 250 mg/day iv on days 1, 2, 3, 4, 5, and 6, none on days 7 and 8, and 250 mg/day every day thereafter for a total of 20 days. Bromocriptine was given for 5 days in doses of 2.5 mg, tid, before onset of fostrolin treatment, and favorably affected clinical course of prostatic malignancy. (18 Refs)

46. HYPERPROLACTINAEMIA IN MALES WITH AND WITHOUT PITUITARY MACROADENOMAS.

Spark RF, Wills CA, O'Reilly G, Ransil BJ, Bergland R
Steroid Res. Lab., Beth Israel Hosp., 330 Brookline Ave., Boston, MA, 02215
Lancet; 2(8290):129-132 1982

To ascertain whether in hyperprolactinemic men pituitary macroadenomas represent the end stage of a disease process wherein the only early symptom is impotence, the features of 16 hyperprolactinemic men with radiological evidence of pituitary macroadenomas were compared with those of 10 hyperprolactinemic men without pituitary macroadenomas. All were impotent and 25 had low serum testosterone levels. The group with pituitary macroadenoma was older (48.1 vs 63.2 yr) and had tolerated impotence for longer (10.4 +-6.0 vs 4.5 +-2.1 yr). Six of them had visual field defects (none in the other group), 14 had hypopituitarism (1 in the other group), and 14 were initially seen for problems other than sexual dysfunction (whereas all 10 without pituitary macroadenomas were seen primarily for evaluation of recent onset of impotence). In the macroadenoma group bromocriptine restored serum prolactin levels in 13 of the 16 and serum testosterone and potency in 5, whereas in the nontumor group it restored serum prolactin levels in all 10 and serum testosterone and potency in 9. (Author abstract) (19 Refs)

47. HYPOPITUITARISM AFTER SURGERY FOR CRANIOPHARYNGIOMA.

Grant DB, Lyen K
Dept. Endocrinology, Hosp. for Sick Children, Great Ormond St., London WC1, England
Childs Brain; 9(3/4):201-204 1982

Endocrinological sequelae in 73 children operated upon for craniopharyngioma are described; results in children treated only by aspiration of the cyst of the tumor are compared with those undergoing direct removal of the lesion. Thirteen cases were treated by cyst aspiration followed by radiotherapy; 58 had partial or complete tumor resection, with either further surgery or radiotherapy for recurrence; and 2 young children with large tumors received no surgical treatment. Five of the 13 cases treated by aspiration died; 4 as a result of tumor recurrence and 1 due to 'coning' a few hr after aspiration. Thirty-six of the 58 children treated by tumor resection were alive at the time of reporting; 16 died; and 6 have been lost to follow-up. There was a very high incidence of endocrine deficits in the group treated by surgery. Fifteen children grew at a normal rate for at least a yr postoperatively, but now 32 children have required growth hormone therapy. Although many children initially treated by tumor resection required further surgery, only one died as a direct result of recurrence. Thirteen deaths were attributed to pituitary deficiency and 2 deaths were of unknown cause. In addition to the deaths, 11 patients required emergency treatment for hypopituitarism. Aggressive surgical management of craniopharyngioma seems to significantly reduce recurrence, but it is associated with a very high incidence of potentially life-threatening pituitary deficits. (4 Refs)

48. PHASE II TRIAL OF A DOPAMINERGIC INHIBITOR IN PREVIOUSLY TREATED MELANOMA PATIENTS (MEETING ABSTRACT).

Neifeld JP, Tormey DC, Baker MA, Meyskens FL, Taub RN
Medical College of Virginia, Richmond, VA, 23298
Proc Am Soc Clin Oncol; 1:C-661 1982

Patients with metastatic melanoma have poor response rates to standard chemo- or hormonal therapy. The unique biochemical pathway present in melanoma resulting in melanin production has been shown to regulate the growth of some melanomas in vitro. Pimozide is a potent neuroleptic of the diphenylbutylpiperidine class; it is a potent dopamine inhibitor and inhibits pituitary releasing factors. We have investigated the value of pimozide in the management of patients with previously treated metastatic melanoma. Twenty-eight patients in four institutions were given 12 mg/day of pimozide; three were inevaluable (two - poor tolerance, one - rapid progression within one week). Four patients had objective responses; 2 complete response (CR) (one - pulmonary metastasis, one - soft tissue, nodal, and liver metastasis), 2 partial response (PR) (one - pulmonary + liver metastasis, one - soft tissue metastasis). Response durations were 5+ and 6 months (CR) and 3+ and 6+ months (PR). Two additional patients had stabilization for 4 and 5 months. Toxicity was moderate and consisted of extrapyramidal manifestations (10 patients) and malaise (4 patients). (no Refs)

49. PROGRESS IN THE HORMONAL DETECTION OF PROLACTIN ADENOMAS.

De Gennes JL, Turpin G, Hesmati H, Carayon A
Service d'endocrinologie Metabolisme, Hopital de la Pitie, Paris, France
Ann Med Interne (Paris); 133(1):12-16 1982

The prolactin hormonal profiles of 13 normal subjects (Group A) were compared with those of 25 patients with radiologically evident pituitary adenomas (Group B), with 13 hyperprolactinemic patients without radiologic signs of an adenoma (Group C), and with 12 patients with secondary hyperprolactinemia (Group D). In Group B, the fasting prolactin level was never less than 100 nanog (ng)/ml. In Group C, the fasting prolactin level was less than 100 ng/ml in 6/13 patients. The prolactin increase following stimulation with thyrotropin releasing hormone (TRH) was 55 ng/ml (520%) in the control subjects (Group A) whereas in Groups B and C, the increase was less than 100%. It is suggested that the TRH test is the best method for determining whether a patient has a prolactinoma. A positive response to the TRH prolactin test does not necessarily rule out the possibility of a tumor, but a nonresponse of a hyperprolactinemic patient to TRH should be considered a definite indication of a prolactin microadenoma even in the absence of neuroradiologic confirmation. (14 Refs) (In FRE)

50. PITUITARY PROLACTINOMAS.

Nabarro JD
Middlesex Hosp., London W1N 8AA, England
Clin Endocrinol (Oxf); 17(2):129-155 1982

A distinction is made between large and small prolactinomas. They have different presenting symptoms, sex distribution and natural history. From a series of 263 patients with obviously enlarged pituitary fossae on lateral skull x-ray, 74 were identified as having chromophobe adenomas and 34 of these are believed to have prolactinomas. A modestly elevated prolactin level with an enlarged pituitary fossa does not mean that the patient has a prolactinoma, the hyperprolactinemia may be due to interference with the hypothalamic prolactin inhibiting mechanism. The special problems of acromegaly are discussed. The presenting symptoms and sex incidence are reviewed. Review of 48 cases of large prolactinoma shows that it may be an unpleasant invasive tumor. Treatment by transfrontal or transphenoidal surgery occasionally results in a cure but are generally disappointing. X-ray therapy is relatively ineffective. Bromocriptine may produce dramatic response but occasional cases are resistant to its action. The value of serial prolactin measurements to monitor tumor growth is stressed. The results of transsphenoidal surgery in 36 patients with higher prolactin levels are reported. The natural history of the small prolactinoma is discussed, the reported incidence of small prolactinomas at autopsy is noted. The advice to be given to a patient with a small prolactinoma who wishes to get pregnant is reviewed. It is suggested that special care should be exercised if the prolactin level exceeds 4,000 mU/l. The floor of the pituitary fossa should be scrutinized on tomograms and the upper limit by computerized tomography. If close observation of the patient is possible through pregnancy, bromocriptine may be given to restore ovulation. If the prolactin level rises excessively or a visual field defect occurs, bromocriptine should be restarted at once. The effect of x-ray therapy on prolactin levels in 15 patients is reported. High prolactin levels are little changed, four patients with lower initial levels achieved normoprolactinemia in 2-6 yr. (50 Refs)

51. BROMOCRIPTINE TREATMENT OF WOMEN WITH SUSPECTED PITUITARY PROLACTIN-SECRETING MICROADENOMAS.

Archer DF, Lattanzi DR, Moore EE, Harger JH, Herbert DL
Dept. Obstetrics and Gynecology, Magee-Womens Hosp., Pittsburgh, PA, 15213
Am J Obstet Gynecol; 143(6):620-625 1982

The present study was designed to investigate the efficacy of bromocriptine in reducing serum prolactin (PRL) levels and in decreasing the size of PRL-secreting microadenomas. Bromocriptine, 5.0 mg, was administered daily for 2 years to 17 women who had galactorrhea, hyperprolactinemia, and hypocycloidal polytomographic evidence suggestive of a pituitary microadenoma. Serum PRL levels were normalized in 16 of 17 women during therapy. Associated with this was resumption of regular menses in 15 of 16 women with menstrual dysfunction and cessation of galactorrhea in 16 of the 17 women. Improvement in the roentgenographic appearance of the sella turcica occurred in two women. No progression in tumor size was found during the course of therapy. Side effects attributed to bromocriptine were minimal, transient, and usually well tolerated. These data suggest that bromocriptine is an appropriate therapeutic modality for PRL-secreting pituitary microadenomas. (Author abstract) (16 Refs)

52. PROLACTIN SECRETING PITUITARY ADENOMAS. EXPLORATIONS AND TREATMENT.

McGregor A, Scanlon M, Hall R
Dept Medicine, Welsh National School Medicine, Heath Park, Cardiff, Wales CF 44 XN, England
Ann Med Interne (Paris); 133(1):51-57 1982

Prolactin secreting adenomas (PSA) account for 32% of secreting pituitary adenomas. Better understanding of the neuroendocrine control of prolactin secretion has permitted earlier diagnosis of PSA. Hormone testing and radiographs are essential elements in establishing a diagnosis of PSA. Although the existence of an abnormal sella does not exclude another pathology, the most probable cause is an expansive pituitary adenoma. Elevated basal levels of prolactin are not sufficient proof of an adenoma and exaggerated response of thyroid stimulating hormone to hormone challenge may be useful in diagnosing such lesions. The three therapeutic modalities which are available to treat pituitary adenomas are surgery, radiotherapy, and chemotherapy. The most encouraging surgical studies have reported prolactin normalization in 70% of patients. Bromocriptine has been shown to inhibit prolactin secretion and tumor growth during the time when it is taken. Reduction in the size of the prolactin macroadenomas has been associated with the disappearance of symptoms and an improvement in pituitary function. (28 Refs) (In FRE)

53. PITUITARY ADENOMAS AND OTHER TUMORS: REVIEW IN PERSPECTIVE OF DIAGNOSIS AND TREATMENT.

Raiti S
Natl. Pituitary Agency, Univ. Maryland Sch. Medicine, Baltimore, MD, 21201
Childs Brain; 9(3/4):147-155 1982

Progress in neuroscience, particularly in the radioimmunoassay identification of anterior pituitary hormones, is reviewed, and approaches to management of pituitary tumors and other tumors are discussed. The first major advance was the discovery of radioimmunoassay for human growth hormone, thyroid-stimulating hormone (TSH) and follicle-stimulating hormone. Newer immunological techniques permitting definitive diagnosis of pituitary tumors were a second step. The third major advance in technology occurred in the area of radiological techniques, including tomography, which may be carried out in thin-section, multidirectional hypocycloidal techniques, and most recently the computerized axial tomography (CT) scan, Endocrinological manifestations often are part of the presenting signs of adenomas in childhood, along with local pressure effects. Pituitary surgery may destroy hormone-producing cells, hence it is essential to differentiate nonfunctioning tumors such as craniopharyngioma, astrocytoma, and aneurysms, or pseudotumors such as the empty sella syndrome, from functioning pituitary tumors. When follow-up demonstrates the necessity, growth hormone, TSH, and gonadotropin replacement therapy should be used. Growth hormone replacement aids in controlling hypoglycemia, a newly recognized problem of postoperative management. Pituitary hormone deficiency can be a complication of other tumors, such as medulloblastoma. (12 Refs)

54. CHARACTERISTICS OF CIRCULATING ERYTHROID COLONY-FORMING CELLS IN NORMAL AND POLYCYTHAEMIC MAN.

Mladenovic J, Adamson JW
Dept. Medicine, Hennepin County Medical Center, 701 Park Ave. South, Minneapolis, MN, 55415
Br J Haematol; 51(3):377-384 1982

Circulating erythroid progenitors from 10 patients with polycythemia vera, nine with secondary polycythemia and 10 normal subjects were studied in culture to determine their frequency, requirements for erythropoietin (ESF) and physical characteristics. Increased numbers of erythroid progenitors were detected in circulation from the patients with polycythemia vera when compared to patients with secondary polycythemia or normals, and 19 +-3% of these progenitors formed endogenous colonies without added ESF. Velocity sedimentation analysis showed that the majority of ESF-dependent erythroid progenitors in all study groups sedimented at 6.46 mm/h. The circulating endogenous erythroid colony-forming cells in polycythemia vera patients sedimented more rapidly. Tritiated thymidine suicide experiments failed to detect significant differences between the percentages of endogenous and ESF-dependent progenitors in DNA synthesis in polycythemia patients and normals. Thus, differences in cell cycle state were not responsible for the more rapid sedimentation of endogenous colony-forming cells. These results further define characteristics of circulating erythroid progenitors in polycythemia vera and normal subjects and suggest that simple culture of peripheral blood cells may be useful in the differential diagnosis of polycythemia. (Author abstract) (27 Refs)

55. REDUCED 3H-DOPAMINE UPTAKE BY BLOOD PLATELETS IN PATIENTS WITH PROLACTIN-SECRETING PITUITARY ADENOMA.

Nicoletti I, Capodicasa E, Santeusanio F, Nenci GG, Brunetti P

Semeiotica Medica e Patologia Medica, Istituti di Clinica Medica, University Perugia, Perugia, Italy

Horm Metab Res; 14(6):310-312 1982

Uptake of 3H-Dopamine by blood platelets was found to be significantly reduced in eight patients with prolactin (PRL) secreting pituitary adenoma in comparison to normal subjects (27.91 +-5.01 nmol/10(11) platelets vs 73.42 +-4.99 nmol/10(11) platelets, p less than 0.001). Since platelet monoamine uptake seems to reflect brain monoaminergic activity, the reduction of dopamine uptake (DAU) in our hyperprolactinemic subjects suggests a defective dopaminergic neurotransmission in patients with PRL-secreting tumors. (Author abstract) (24 Refs)

56. RECENT ADVANCES IN HORMONAL DETECTION OF PITUITARY SOMATOTROPIC ADENOMAS.

Turpin G, Heshmati H, De Gennes J

Service d'Endocrinologic-Metabolisme, Groupe Hospitalier Pite-Salpetriere, 47-83, boulevard de l'Hopital, F 75651 Paris, France

Ann Med Interne (Paris); 133(1):17-22 1982

Diagnostic hormonal tests were performed in 15 patients with acromegaly (8 men, 24-59 yr old, and 7 women, 27-62 yr old). The test group included 14 patients with macroadenomas of which 12 had been treated surgically and 2 were treated only with radiotherapy. One patient with a microadenoma was not treated. Following iv injection of thyrotropin releasing hormone (TRH), growth hormone (GH) increased in 9/15 cases between 50-2,650%. Prolactin increased in 13 cases between 50 and 900%. Following stimulation with luteinizing hormone releasing hormone, GH increased (54%) in one case, and prolactin did not increase in any cases. Following stimulation with Bromocriptine (BR), GH was blocked in seven cases between 52 and 97%. Prolactin was blocked in 11 cases. In five patients who had a positive response to TRH stimulation with BR followed by TRH led to secondary increase in prolactin secretion in response to TRH. The most reliable diagnostic tests are assays of basal GH and somatomedin levels, and the absence of blocking of GH by glucose. The tests described above could be valuable in the rare cases when the results of biological tests are inconclusive. (40 Refs) (In FRE)

57. POST-THERAPEUTIC HORMONAL SURVEILLANCE OF SOMATOTROPIC ADENOMAS.

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Ann Med Interne (Paris); 133(1):38-41 1982

Following treatment of somatotropic adenomas, acromegaly should be monitored by various tests. Growth hormone levels with provoked hyperglycemia are not sufficient in affirming the cure of acromegaly. If the plasma level is less than 5 nanog/ml, a thyroid releasing hormone (TRH) test is required. If the TRH test is negative, a complete growth hormone test or an insulin like growth factor test is useful. All these tests are necessary in order to assess the usefulness of complementing cobalt therapy. (12 Refs) (In FRE)

58. MULTIPLE ENDOCRINOPATHIES.

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Afdeling klinische endocrinologie, Academisch Ziekenhuis, Utrecht, The Netherlands

Ned Tijdschr Geneeskd; 126(11):477-482 1982

Studies on multiple endocrine neoplasia (MEN syndrome) are reviewed. Type 1 of MEN syndrome is diagnosed in 4% of all patients with insulinomas and in 20-30% of all patients with Zollinger-Ellison syndrome caused by gastrinoma. Prolactinoma occurring in patients with Type 1 MEN syndrome has the same clinical picture as solitary hypophyseal tumors. Medullary carcinoma of the thyroid gland in patients with Type 2 MEN syndrome is always multifocal and characterized by hyperplasia of C cells. Pheochromocytoma in patients with Type 2 MEN syndrome is multiple, bilateral and often extraadrenal. (12 Refs) (In DUT)

59. THYROXINE AND TRIIODOTHYRONINE EQUILIBRIUM IN HUMAN NORMAL AND LEUKEMIC LEUKOCYTES.

Notario A, Petrucci E, Zocchi MT, Pricca D

Via Severino Boezio 1, 27100 Pavia, Italy

J Nucl Med Allied Sci; 26(1):9-14 1982

Thyroxine (T4), triiodothyronine (T3), and reverse T3 were measured in leukocytes isolated from the peripheral blood of 20 normal subjects, 15 patients with chronic myeloid leukemia (CML), 13 with acute myeloid leukemia (AML), 12 with chronic lymphatic leukemia (CLL), and 7 with acute lymphatic leukemia (ALL) to assess whether an alteration of the cellular metabolism and main equilibrium of the main thyroid hormones exist in leukemic cells. In CML a decrease in both T3 and T4 was constantly observed, so that the T3/T4 ratio was reduced to 1.11 +-0.21 vs 1.88 +-0.39 in normal subjects. Very low values were observed in AML (0.45 +-0.15). The decrease in T3 and T4 values in AML was greater when expressed per cell vol. Similar changes in the T3 and T4 content were observed in CLL and ALL. A significant decrease of T3 and T4 uptake by leukocytes was observed in all types of leukemia except for 125I-T3 in CML. The mean values obtained are presented, showing the greatest reduction in CLL. Different explanations for the reduction were proposed such as an increase of the intracellular turnover of the thyroid hormones or a reduced uptake of the hormones secondary to an alteration of the membrane and cellular receptors. (28 Refs)

60. CLINICAL VALUE OF THYROGLOBULIN (HTG) RIA IN FOLLOW-UP OF DIFFERENTIATED THYROID CARCINOMA (MEETING ABSTRACT).

Bottger I, Kanitz W, Pabst HW
Nuclearmedicine Clinic and Policlinic, Technical University Munich, Munich, W. Germany
J Nucl Med; 23(5):97 1982

Interference by endogenous hTg antibodies, TSH (thyroid stimulating hormone) induced hTg stimulation and recent reports of false negative/positive results are parts of an ongoing controversy of the hTg RIA's (radioimmunoassays) clinical value being reassessed in this study. All patients investigated had undergone total thyroidectomy and subsequent radioiodine therapy for differentiated thyroid carcinoma. A recovery was done in each serum by addition of 80 ug hTg. Radioiodine whole body scans were performed with 1-2 mCi I-131. HTg antibodies were found in 7%, 7 of these 11 sera demonstrating an unacceptable hTg recover of worse than +/-50%. Four hundred and thirty-three sera without detectable antibodies showed recoveries of up to +/-15% in 62%, +/-16-30% in 19%, +/-31-50% in 9% and worse that +/-50% in 10%. Twelve sera without detectable antibodies, with a recovery of better than +/-50% in 7 and hTg levels between 96 and 378 ug/l consistenting revealed higher hTg concentrations on 1:5 and 1:10 dilution with 0 hTg standard. TSH-induced hTg stimulation could only be observed in 4 of 31 patients without but in 7 of 11 with metastases, which, however, did not affect the diagnosis. There were only one questionably false negative and 3 false positive hTg determinations in 30 patients with and 32 without metastases being opposed by 7 false negative radioiodine whole-body scans. (no Refs)

61. FAMILIAL HYPOCALCIURIC HYPERCALCEMIA: THE RELATION TO PRIMARY PARATHYROID HYPERPLASIA.

Marx SJ, Spiegel AM, Levine MA, Rizzoli RE, Lasker RD, Santora AC, Downs RW, Aurbach GD, Young J, Pallotta J, Garber JR, Flier J
NIH, Bldg. 10, Rm. 9-C-101, Bethesda, MD, 20205
N Engl J Med; 307(7):416-426 1982

Familial hypocalciuric hypercalcemia (FHH) is reviewed on the basis of studies of large families. FHH is an autosomal dominant characteristic. Expression of FHH is lifelong. The severity of symptoms varies and may be mild. In kindreds with FHH, hypercalcemic members more frequently show fatigue, weakness, mental problems, polydipsia, polyuria, arthralgia, and headache than normocalcemic members. Signs attributable to FHH are rare. Parathyroid surgery is generally unsatisfactory for treatment of FHH. Regulation of serum calcium in FHH is apparently different from that in typical primary hyperparathyroidism (TPH). Total concentration and the ionized fraction of serum calcium are similar in FHH and TPH. Approx 50% of patients with FHH also have increased serum magnesium concentrations. Renal function is well-maintained in FHH. Renal resorption of calcium apparently is regulated by factors other than parathyroid hormone. A high level of immunoreactive parathyroid hormone in the plasma, increased mass of the parathyroid gland, and severe primary hyperparathyroidism in neonates indicate that parathyroid dysfunction is an integral feature of FHH. Mild parathyroid hyperplasia is a consistent feature. Other hereditary causes of primary parathyroid hyperplasia include neonatal severe primary hyperparathyroidism and familial multiple endocrine neoplasia. The prevalence of FHH is unknown. Most patients require no active treatment, since the rate of morbidity is low. Indications for intervention include severe primary hyperparathyroidism in neonates, which may be life-threatening, and pancreatitis. FHH may result from dysfunction in a single metabolic pathway. (92 Refs)

62. THYROID FUNCTION AFTER RADIOTHERAPY AND LARYNGECTOMY FOR CARCINOMA OF THE LARYNX (MEETING ABSTRACT).

Palmer BV, Pittam M, Shaw J
Royal Marsden Hospital, London, England
Clin Oncol; 8(1):79 1982

Total Thyroxine (T4) and Thyroid Stimulating Hormone (TSH) levels were measured in 37 patients who had previously had carcinoma of the larynx treated by radiotherapy and laryngectomy. Thirty per cent had total T4 levels below the lower limit of normal. A further 40% had results in the low normal range. Forty per cent of patients had raised TSH levels, 90% of these having low or low normal T4 levels. The histology of the thyroid gland was normal in all 37 patients. Sequential Thyroid Function Tests after surgery show that it takes about 4 to 5 months before the lowest serum levels are obtained. There is only a slight increase in serum T3 and T4 levels after this time. It is questioned whether a hemithyroidectomy should be a standard procedure when performing laryngectomies. (no Refs)

63. MALIGNANT POSTERIOR FOSSA TUMORS OF CHILDHOOD-ENDOCRINE FUNCTION-STATUS POST RADIATION AND CHEMOTHERAPY (MEETING ABSTRACT).

Oberfield SE, Pareira J, Allen JC, Jereb B, Levine LS, Miller DR, New MI
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Pediatr Res; 16(4,part2):210A 1982

Eleven patients (6 male, 5 female) who had received standard neuraxis radiation with (7) or without (4) chemotherapy for treatment of posterior fossa tumors (medulloblastoma (10), ependymoma (1)), had hypothalamic-pituitary target organ axis evaluation at 3-53 months after completion of treatment. The age range at initiation of treatment was 3 7/12-23 8/12 yrs and age range at time of evaluation was 4 1/12-24 1/2 yrs. The radiation treatment consisted of approximately 3600 rads to the neuraxis with a 1500 rad boost to the posterior fossa. The approximate mean radiation dose to the hypothalamic-pituitary region and thyroid gland were 3600 and 2300 rad respectively. In 9/11 patients the skeletal age was within one year of the chronological age. Growth hormone reserve was deficient in 5/11. Somatomedin C was decreased for age in 2/9 patients. Cortisol response to insulin-induced hypoglycemia was inadequate in 1/7. TSH (thyroid stimulating hormone) response to TRH (thyrotropin releasing hormone) testing was performed in 9 patients and was normal in 3, compatible with primary thyroid dysfunction in 5 and suggestive of hypothalamic dysfunction in 1. One patient developed abnormal thyroid function 12 mos after an initially normal evaluation. Since endocrine evaluation was not obtained prior to therapy, we cannot be certain that the described abnormalities were a consequence of treatment. (no Refs)

64. GROWTH AND HORMONAL STATUS OF CHILDREN TREATED FOR BRAIN TUMOURS.

Shalet SM

Dept. Endocrinology, Christie Hosp., Manchester, England

Childs Brain; 9(3/4):284-293 1982

Radiation-induced growth hormone (GH) deficiency, and hypopituitarism in children treated for brain tumors not directly involving the hypothalamic-pituitary axis are reviewed, and the site of radiation-induced damage and mechanism of GH deficiency causing growth retardation are discussed. Radiation has been associated with impaired GH response, but children having intact hypothalamic-pituitary function with brain tumors requiring either partial or complete neurosurgical removal showed no significant difference in GH response after treatment, suggesting that neither the mere presence of a tumor in the brain nor neurosurgery could account for the GH deficiency observed in irradiated patients. Studies of 20 adult patients who previously had received irradiation for brain tumors showed an unusual number with shorter than normal stature, and three had an elevated basal serum thyroid-stimulating hormone level; no other abnormality in anterior pituitary function was observed. The major site of damage is apparently the hypothalamus. GH is the first hormone to be affected by radiation-induced damage to the hypothalamic-pituitary region. In one study 12/13 irradiated children grew poorly in the first yr, but those with lowered GH secretion grew just as poorly as the others. Monitoring of growth after treatment, with appropriate supplemental human GH therapy is recommended for all children treated for a brain tumor. (27 Refs)

65. AMINOGLUTHETIMIDE (AG) AND HIGH-DOSE MEDROXYPROGESTERONE ACETATE (MPA) IN ADVANCED BREAST CANCER (MEETING ABSTRACT).

Beex L, Pieters G, Smals A, Koenders A, Benraad T, Kloppenborg P

Department of Endocrinology and Laboratory for Experimental and Chemical, Endocrinology University Hospital, Nijmegen, The Netherlands

International Symposium on Medroxyprogesterone Acetate, February 24-26, 1982, Geneva, Switzerland. Farmatalia Carlo Erba 91 pp., 1982.

In a pilot study 8 postmenopausal patients with very advanced breast cancer, refractory to standard hormono- and chemotherapy have been treated with AG, 4 x 250 mg daily orally, combined with MPA 500 mg im daily for 28 days, followed by 500 mg im two times per week. Estradiol receptor activity of the tumor was positive in 5, negative in one and unknown in 2 patients. Most serious side effects of this drug combination were dizziness and lethargy during the first week of therapy. Other side effects were mild, corresponding to those well-known for each of the two drugs. Two patients required mineralo-corticoid medication. No patients received gluco-corticoid substitution. In all of the 8 patients plasma-ACTH, cortisol and aldosterone levels decreased to borderline or undetectable values. In 4 of 8 patients serum TSH (thyroid stimulating hormone) levels increased. Objective tumor regression has been observed in 4 of 8 patients for 2+, 4, 7 and 10+ months, whereas in one patient there was stabilization of disease for 3+ months. The patient without ER activity in her tumor did not respond to therapy. In conclusion: AG combination with HD-MPA seems to be an effective treatment for postmenopausal patients with ER positive very advanced breast cancer. (no Refs)

66. EFFECT OF SULPIRIDE ON PLASMA TSH SECRETION IN VARIOUS HYPOTHALAMO-PITUITARY DISORDERS.

Sasaki A

Second Dept. Internal Medicine, Tohoku Univ. Sch. Medicine, Sendai, Japan

Nippon Naibunpi Gakkai Zasshi; 58(3):210-224 1982

Effects of sulpiride, a dopamine antagonist, were studied in 87 patients with various hypothalamo-pituitary disorders to clarify the question of hypothalamic dopaminergic participation in the secretion of thyroid stimulating hormone (TSH). A human TSH radioimmunoassay was used to measure levels of TSH in the plasma. The mean TSH level increased by an increment of 1.01 +-0.17 microUnits (uU)/ml in 18 normal subjects after injection of the sulpiride. Compared to these increases in TSH levels in normal subjects, those in patients with pituitary adenomas were much higher, with mean max increments as follows: 1.65 +-0.24 uU/ml in 21 acromegaly patients; 2.63 +-0.55 uU/ml in 23 nonfunctioning pituitary adenoma patients; and 4.49 +-0.70 uU/ml in 17 prolactin-producing pituitary adenoma patients. No changes in levels of TSH were observed after administration of sulpiride to nine patients who had hypothalamic tumors and hyperprolactinemia. The findings suggested that patients with prolactin-producing pituitary adenoma and those with other pituitary adenomas show increased dopaminergic inhibitory influence on TSH secretion. The sulpiride test was thought to be applicable to differential diagnosis of hypothalamo-pituitary disorders. (41 Refs) (In JPN)

67. RADIONUCLIDE BONE AND LIVER SCANNING IN PATIENTS WITH MEDULLARY CARCINOMA OF THE THYROID GLAND (MEETING ABSTRACT).

Johnson DG, Coleman RE, McCook TA, Dale JK, Wells SA

Duke University Medical Center, Durham, NC

J Nucl Med; 23(5):20 1982

The purpose of this study was to determine the results of radionuclide bone and liver scans in patients with medullary carcinoma of the thyroid gland (MCT), an uncommon malignancy known for early metastases. Thirty-four patients with surgically proven MCT and elevated serum thyrocalcitonin levels had technetium-99m medronate bone and/or sulfur colloid liver scans for suspected metastases. Liver scans were available in 32 patients and bone scans in 30 patients. Skeletal radiographs were available in 16 patients who had bone scans. Liver scans demonstrated focal metastatic lesions in nine of 32 patients. Eight were hepatic and one was splenic. Bone scans were positive for metastases in 9 of 30 patients. Five of these 9 patients demonstrated only skeletal lesions; 2 demonstrated only the presence of Tc-99m medronate uptake within hepatic or other soft tissue metastases; the remaining 2 demonstrated both skeletal and non-skeletal metastases. No detectable radiographic calcification was present in any of the 4 patients in whom non-skeletal metastases were seen on bone scans. Of the 16 patients who had both bone scans and radiographs, 3 patients demonstrated skeletal metastases, and these lesions were recognized on both examinations. Radionuclide bone and liver scans frequently demonstrate metastatic lesions in patients with known medullary carcinoma of the thyroid gland. (no Refs)

68. RADIOIMMUNOASSAY OF URINARY CALCITONIN IN NORMAL SUBJECTS AND IN PATIENTS WITH MEDULLARY CARCINOMA OF THE THYROID.

Morimoto S, Onishi T, Okada Y, Lee S, Imanaka S, Fukuo K, Kono H, Kumahara Y

Dept. Medicine and Geriatrics, Osaka Univ. Medical Sch., Fukushima-ku, Osaka 553, Japan

Endocrinol Jpn; 29(1):1-10 1982

A simple radioimmunoassay (RIA) technique for measuring calcitonin (CT) in the urine was tested on 32 normal subjects (24 males and 8 females, 21-81 yr old) and 11 patients with medullary carcinoma of the thyroid (MCT). Plasma and urine samples were obtained in the morning after overnight fasting. Urine tests were generally performed on the second morning sample. Twenty-four-hr urine samples were obtained from 20 normal subjects on the day before blood sampling. Three normal volunteers underwent infusion of 4 mg calcium gluconate/kg body wt iv over a 1-min period. Plasma was sampled before and 2, 5, 30, and 60 min after infusion. Urine was sampled at 15-min intervals from 30 min before until 60 min after the start of infusion. Three normal subjects underwent infusion of 0.5 mg human CT iv over a 1-min period. Plasma was sampled before and 2, 5, 15, 30, 60, and 120 min after infusion. Recovery of synthetic human CT in the RIA was 86.1 +-6.2%; the intra-assay and inter-assay coefficients of variation were 5.9% and 8.2%, respectively. Among the 11 patients with MCT, urinary levels of CT exceeded plasma levels by a factor of 3.4-20.8 and were strongly correlated with the plasma levels. Among normal subjects, urinary CT exceeded plasma CT by a factor of 0.41-5.1 and was weakly correlated with plasma levels. Urinary CT in normal subjects rose after calcium gluconate infusion, apparently in response to rising endogenous CT in the plasma; urinary CT also rose after infusion of exogenous CT. Gel filtration disclosed larger molecular forms of CT in MCT patients and in normal subjects after infusion. The RIA assay of urinary CT is evidently useful for diagnosis of MCT and evaluation of CT metabolism in normal subjects. (20 Refs)

69. MEDULLARY CARCINOMA OF THE THYROID.

Paches AI, Propp RM, Abdullin NA, Anokhin BM

Center for Oncology Res., USSR Acad. Medical Sciences, Moscow, USSR

Vopr Onkol; 28(5):77-82 1982

The paper deals with a study of 42 cases of medullary carcinoma which accounts for 12.6% of all forms of thyroid cancer. The female-to-male ratio was 1.3:1, mean age 45 yr. Medullary carcinoma occurs sporadically in cases of familial endocrine syndrome. A case of Sipple's syndrome is reported. Medullar carcinoma is a hormonally-active tumor which produces calcitonin, the latter serving as a tumor market for this carcinoma. Medullary carcinoma is characterized by bilateral involvement of the thyroid, which is more frequent in cases of familial disease, and a high rate of incidence of regional metastases (82.5%). Apart from clinical diagnostic means, the disease is chiefly identified cytologically and by calcitonin assays in blood plasma. It is mainly treated by surgery; 5-and 10-yr survival rates are 87.2 and 80%, respectively. (Author abstract) (16 Refs) (In RUS)

70. HORMONAL SURVEILLANCE OF CORTICOTROPIC ADENOMAS.

Luton JP, Kuhn JM, Bricaire H

Centre de Recherches en Endocrinologie, Hopital Cochin, 27, rue du Faubourg-Saint-Jacques, F 75674 Paris, France

Ann Med Interne (Paris); 133(1):42-44 1982

In 27 cases of post-therapeutic surveillance of corticotropic adenomas, an adenoma was found in 22 cases. In four other patients, pathological tissue was found during pituitary exploration and in the other patients, meningocele was discovered. The evolution of corticotropic hormonal surveillance necessitates precise and repeated postoperative hormonale surveillance. Since there are no absolute criteria for differentiating autonomous corticotropic adenomas from corticotropic hyperplasia, hormonal surveillance becomes essential in post-therapeutic cases of corticotropic adenomas. (10 Refs) (In FRE)

71. THE CONTRIBUTION OF HORMONE TESTING IN THE DIAGNOSIS OF CORTICOTROPIC PITUITARY ADENOMAS.

Kuhn JM, Bertagna X, Girard F

Laboratories d'Explorations fonctionnelles, Hoptial Trosseau, 25, avenue du Docteur-Arnold-Netter, F 75571 Paris, France

Ann Med Interne (Paris); 133(1):23-25 1982

Hormone tests with thyrotropin releasing hormone, ACTH, and lipotropic hormone were carried out to determine the role of pituitary adenomas in patients with Cushing's (CD) disease. None of the tests were conclusive in determining definitive correlations between pituitary adenomas and CD, and none of the tests was a reliable indicator of surgically effectiveness for the treatment of CD caused by pituitary adenomas. (15 Refs) (In FRE)

72. PEPTIDE HORMONE LH, FSH, TSH, PROLACTIN, BETA-HCG, AND PTH IN PATIENTS WITH UROGENITAL TUMORS.

Dunzendorfer U, Drahovsky D, Schmidt-Gayk H

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Onkologie; 4(4):188,190-192 1981

Serum levels of the peptide hormones LH, FSH, TSH, prolactin, beta-HCG and PTH are observed to significantly modulate in patients with urogenital tumors. Beta-HCG appears elevated in patients with choriocarcinoma, teratoma and embryonal carcinoma and is shown to increase serum prolactin. TSH and prolactin are measured in pathological range in patients with renal carcinomas. Following nephrectomy serum TSH persists in high levels only in patients with advanced diseases, while PTH is more frequently suppressed in these patients. Serum LH and prolactin show a more distinct change of values in infiltrating bladder cancer, when compared to that of noninvasive bladder carcinomas. Prostate benign hyperplasia and cancer demonstrate similar ranges for peptide hormones, that will be changed by estrogen treatment in its LH, TSH and prolactin pattern. Serum levels of peptide hormones are affected by a complex system of ectopic hormone production, synthesis of peptide analogues, metabolic changes due to age and treatment. (Author abstract) (14 Refs) (In GER)

73. BLOOD HORMONE LEVELS RELATED TO STAGES AND GRADES OF PROSTATIC CANCER.

Holsaeter PA, Haukaas S, Bakke A, Holem L, Segadal E, Thorsen T
Section Urology, Dept. General Surgery, Univ. Bergen, 5016 Haukeland Sykehus, Bergen, Norway
Prostate; 3(4):375-381 1982

Blood hormone levels were determined in 100 patients (50-88 yr old) with different stages and grades of prostatic cancer. As to stages, 14 patients were in I, 25 in II, 25 in III, and 36 in IV. Within each stage, prostatic cancer was graded as highly differentiated carcinoma (50), moderately differentiated carcinoma (31), and poorly differentiated carcinoma (19). The blood samples were analyzed for follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), testosterone, estradiol, and sex hormone binding globulin (SHBG). Analysis of blood hormone levels in the patients with different stages and grades of prostatic carcinoma showed no specific hormonal pattern. The majority of patients had normal values of FSH, LH, and PRL, although PRL levels had a tendency to increase with increasing stage of the disease. Most of testosterone values were in a lower range of normal, compared with a significant number of estradiol levels that exceeded the normal range. Higher than normal SHBG values were observed in the patients with Stage I and Stage IV disease. (21 Refs)

74. CLINICAL IMPLICATIONS OF CELL METAPLASIA AFTER PROSTATECTOMY.

Baranyai E
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Int Urol Nephrol; 14(2):173-176 1982

Cell metaplasia was studied in men who had undergone prostatectomy. Epithelial metaplasia with hyperplasia of the prostate is an inflammatory complication and possible source of complications, but is not a source of carcinogenesis. Malignant degeneration of metaplasia with atypia is not affected by hormone treatment. Patients with atypical metaplasia should be followed up carefully. Microscopic evidence of occult carcinoma requires orchiectomy and hormone treatment. (12 Refs)

EFFECTS ON NORMAL AND NEOPLASTIC CELLS AND TISSUES

75. PROPRANOLOL BLOCKS NOREPINEPHRINE-STIMULATED PHOSPHOLIPID METHYLATION IN ARACHIDONIC ACID-LABELLED NEUROBLASTOMA CELLS (MEETING ABSTRACT).

Birkle DL, Ellis EF
Medical College of Virginia, Richmond, VA, 23298
Fed Proc; 41(3):1046 1982

The effects of Norepinephrine (NE) on N-methylation of phosphatidylethanolamine (PE), arachidonic acid (AA) distribution in phospholipids (PLs) and conversion of AA to prostglandins (PGs) and hydroxy-eicosatetraenoic acids (HETEs) were studied in the intact murine neuroblastoma clone, Neuro-2A. NE (5uM) stimulated incorporation of 3H-S-adenosylmethionine into phosphatidylcholine (PC) and N,N-dimethyl PE (PDE). Propranolol blocked this effect and caused an accumulation of N-monomethyl PE. The major PLs labelled by 14C-AA were PC and PE. NE (5uM) enhanced total incorporation of 14C-AA into PLs and increased the percent label of PC and PDE and decreased the percent label in PE. This effect was reversible by washing out NE. These results indicate a reversible, beta-receptor-mediated stimulation of PE N-methylation in the Neuro-2A cell. NE (0.5 mM) stimulated synthesis of PGs, with PGE2, PGF2 and their 15-keto-13,14-dihydro metabolites being the major cyclooxygenase products formed. HETE synthesis was inhibited by NE and abolished by a lipoxygenase inhibitor, eicosatetraynoic acid (10uM). In summary, the Neuro-2A cell actively metabolizes AA and responds to NE with stimulation of PE N-methylation, increased PG synthesis and decreased HETE synthesis. (no Refs)

76. DNA DAMAGE AND SELECTIVE TOXICITY OF DOPA AND ASCORBATE: COPPER IN HUMAN MELANOMA CELLS.

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Cancer Res; 42(9):3783-3788 1982

Six of eight human melanoma lines showed increased sensitivity to killing by dopa and by ascorbate:copper compared with two fibroblast strains and four other human cell lines of nonmelanoma origin. Catechol, epinephrine, and alpha-methyldopa, but not 5,6-dihydroxyindole, exhibited a similar degree of selectivity. Toxicity was greatly reduced when brief exposure times or high cell densities were used. Depending upon culture conditions, melanoma cells accumulated more [3H]dopa- and [14C]ascorbate-derived isotopic label within the first 5 min than fibroblasts, but after 1 hr this difference was less marked. The catalase activity in melanoma cells was not less than that in fibroblasts. Using two independent methods to determine each type of damage, dopa and ascorbate:copper were found to induce DNA breaks in both cell types but not DNA repair synthesis or DNA interstrand cross-links. More DNA breaks were found in melanoma cells (two lines) than in fibroblasts. Semiconservative DNA synthesis was inhibited immediately, recovered within 6 hr, and in melanoma cells was again inhibited after 24 hr. RNA synthesis was inhibited less than DNA synthesis. Human cell lines with differential sensitivity to alpha-radiation, ultraviolet light, cross-linking agents, or monofunctional alkylating agents exhibited normal survival levels when treated with dopa or ascorbate:copper. (Author abstract) (36 Refs)

77. HORMONAL RESPONSIVENESS OF THE HUMAN MALIGNANT MELANOMA CELL LINE HS0294 (MEETING ABSTRACT).

Lawson DH, Richmond A, Chawla PK, Nixon DW
Emory University School of Medicine, Atlanta, GA, 30322
Fed Proc; 41(3):736 1982

Both fibroblast growth factor (FGF, 50 ng/ml) and follicle stimulating hormone (FSH, 0.5 ug/ml) modestly enhance the incorporation of (3H)-thymidine into DNA in Hs0294 melanoma cels growing in serum-depleted medium. FSH treated cultures incorporated 39% more (3H)-thymidine than did controls and FGF treated cultures incorporated 18% more (3H)-thymidine than did controls. In contrast, insulin (5 ug/ml), transferrin (1 and 5 ug/ml), progesterone (2 x 10-8M), testosterone (2 x 10-8M), luteinizing hormone releasing factor (LRF, 1 ng/ml) epidermal growth factor (EGF, 5 and 15 ng/ml) and fetal calf serum (FCS, 0.75-200 ug of protein and 10%) did not stimulate (3H)-thymidine incorporation when added as single agents. When these same concentrations of insulin, transferrin, progesterone, LRF and FSH were added simultaneously, the hormonally treated cultures incorporated 100% more (3H)-thymidine into DNA than did control cultures. Elimination of FSH or any one of the other hormones in this combination decreased (3H)-thymidine incorporation only slightly. These results demonstrate that human melanoma cells exhibit a hormonal response similar to that reported for mouse melanoma cells. (no Refs)

78. EFFECT OF INSULIN AT DILUTION ENDPOINT CONCENTRATIONS ON MACROMOLECULAR SYNTHESIS IN NORMAL MOUSE MAMMARY AND HUMAN BREAST CANCER EPITHELIAL CELLS.

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Biochim Biophys Acta; 720(4):346-355 1982

Employing defined media conditions, the insulin sensitivities of mouse mammary gland epithelial cells in primary culture and MCF-7 human mammary epithelial cells were determined. Insulin stimulated the rates of [3H]uridine incorporation into RNA and [3H]leucine incorporation into protein in both primary mouse mammary gland epithelial cell cultures and MCF-7 cell cultures at concentrations approximating the dilution endpoint of the hormone (10(-21) M). Insulin stimulated the rate of [3H]thymidine incorporation into DNA in primary mouse mammary gland epithelial cells at the dilution endpoint concentrations. However, MCF-7 cells required insulin concentrations 100-1,000x that necessary in mouse mammary epithelial cultures to elicit an increased rate of [3H]thymidine incorporation into DNA. Evidence is presented which suggests that the increased rates of uptake of [3H]uridine, [3H]thymidine and [3H]leucine into their respective precursor pools is not responsible for the apparent stimulation of RNA, DNA and protein synthesis. (Author abstract) (24 Refs)

79. FEEDING RESPONSE OF TUMOR-BEARING RATS TO INSULIN AND INSULIN WITHDRAWAL AND THE CONTRIBUTION OF AUTONOMOUS TUMOR DRAIN TO CACHECTIC DEPLETION.

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Cancer Res; 42(9):3642-3647 1982

The Walker 256 carcinosarcoma growing in Sprague-Dawley rats and the Morris 5123 hepatoma growing in Buffalo rats both produce cachexia but have widely differing patterns of host metabolism and tumor growth. Both organisms respond to exogenous insulin with increased food intake and rate of weight gain of host. The insulin treatment response of food intake was 1.5 to 2x and of body weight gain was 2 to 3x that of tumor-free controls. Insulin does not accelerate tumor growth. On withdrawal of insulin, the reactive hypophagia seen in tumor-free rats does not occur in tumor bearers, and the host weight does not return to the expected untreated value as it does in tumor-free rats. Most of the weight gained during insulin treatment of tumor bearers above that gained by tumor-free rats is retained after withdrawal of insulin. A computer model based on the inference from these results, that the tumor-bearing host is blind to body weight error, indicates that this abnormality of feeding control could account for only about one-third of the observed depression of host weight and food intake. (Author abstract) (28 Refs)

80. RESPONSES OF HUMAN CHONDROSARCOMAS TO N6-MONOBUTYRYL CYCLIC AMP, PROSTAGLANDIN A1 AND SERUM FACTORS (MEETING ABSTRACT).

McCumbee WD, Lebovitz HE
Duke Medical Center, Durham, NC, 27710
Fed Proc; 41(3):736 1982

In cartilage, RNA synthesis is stimulated by serum from intact (Norm) and growth hormone-treated hypophysectomized (GH-Rx) rats but not by serum from untreated hypophysectomized (Hypx) rats. N6-monobutyryl cyclic AMP (MBcAMP) either stimulates (embryonic chick cartilage) or has no effect (rat costal cartilage) on RNA synthesis, whereas prostaglandin A1 (PGA1) profoundly inhibits the synthesis of RNA. The present study investigated the in vitro regulation of [3H]uridine incorporation into RNA of 5 human chondrosarcomas to determine if malignant human chondrocytes are under similar metabolic and hormonal regulation. Uridine incorporation into RNA was stimulated by growth hormone-dependent serum factors in one tumor and by growth hormone-independent factors in 2 tumors. Two tumors were unresponsive to serum stimulation. PGA1 markedly inhibited uridine incorporation into RNA in all 5 tumors (56 to 80%). MBcAMP inhibited uridine incorporation in 4 of the 5 tumors by 32 to 50%. The data indicate that chondrosarcoma cells. This is similar to its effect on normal chondrocytes. MBcAMP regulation differs from that observed in normal chondrocytes: MBcAMP inhibited RNA synthesis in most of the chondrosarcomas studied. Tumor responses to serum factors vary among individual tumors with one responding similarly to normal cartilage and the others not. (no Refs)

81. STIMULATION OF B16 MELANOMA ADENYLATE CYCLASE ACTIVITY BY MSH RELATED PEPTIDES (MEETING ABSTRACT).

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Br J Dermatol; 106(1):115 1982

There is now evidence that the melanosome dispersing activity of MSH depends on two 'message' sequences, corresponding to positions 5-9 (Glu-His-Phe-Arg-Trp) and 10-13 (Gly-Lys-Pro-Val NH(2)) of the molecule. As well as this rapid action on amphibian melanophores, MSH and related peptides stimulate melanogenesis both in amphibian skin and in mammalian melanocytes and melanoma cells through stimulation of tyrosinase activity. This action is known to be mediated through cyclic AMP dependent mechanisms. The ability of alpha-MSH, beta-MSH and related ACTH peptides to stimulate an adenylate cyclase enzyme in a highly pigmented B16 melanoma cell line has recently been investigated in our laboratory. The peptides alpha-MSH, beta-MSH 1-39, ACTH 1-24 all stimulated the enzyme to a similar maximal extent and with similar potency, although ACTH 1-39 was slightly less potent. The heptapeptide sequence ACTH 4-10 was, however, only a partial agonist of this enzyme as was an 11 amino acid synthetic MSH preparation. Our data suggest that at least part of the heptapeptide sequence ACTH 4-10 is necessary for the activation of the receptor-linked adenylate cyclase system but that this sequence alone does not contain all of the structural features required for full activation of the enzyme. It could well be that melanoma cells recognize the same two 'message' sequences on the MSH peptide that determine the melanosome dispersing activity and it is possible that both sequences are required for full activation of adenylate cyclase and hence melanogenesis. However, while the sequence ACTH 14-24 reduces the melanosome dispersing action of ACTH 1-13 (alpha-MSH), in the frog melanophore, in our studies using the B16 melanoma, the adenylate cyclase response to ACTH 1-13 was reduced by the sequence ACTH 25-39. Furthermore, melanotrophic potentiating factor (MPF), which by itself failed to activate the B16 adenylate cyclase receptor, had no effect on the response to alpha-MSH whereas it has been reported to potentiate the actions of alpha-MSH in lizard skin and the melanogenic response to alpha-MSH in hamster follicles. (6 Refs)

82. THEOPHYLLINE AND MELANOCYTE-STIMULATING HORMONE EFFECTS ON GAMMA-GLUTAMYL TRANSPEPTIDASE AND DOPA REACTIONS IN CULTURED MELANOMA CELLS.

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J Invest Dermatol; 79(1):57-62 1982

Gamma-glutamyl transpeptidase (GGT), an enzyme of the gamma-glutamyl cycle, was demonstrated in three of six cell lines derived from a single B16 murine melanoma. Its activity in these cells varied a great deal, appeared to be correlated with the developmental cycle of the cells, and was greatest in young, actively melanogenic cells. Generally, the activity seemed parallel to that of tyrosinase, an enzyme specific for melanin synthesis. The levels of both enzymes tended to decline with prolonged in vitro cultivation, but could be readily renewed after one animal passage. The three cell lines that were GGT-negative were nonpigmented and DOPA-negative; so was a nonmelanogenic and nonmelanocytic rhesus cell line. Melanocyte-stimulating hormone (MSH) and theophylline both enhanced pigmentation in murine melanoma cells. The mechanisms of their action apparently differed. We found that theophylline increased both DOPA- and GGT-reactive cells, whereas MSH only increased DOPA-reactive cells. All three GGT-positive lines were tumorigenic, and two GGT-negative lines were not tumorigenic. Our observations suggest that GGT plays a role in the melanin biosynthetic pathway and that its activity is greater in melanoma cells that are tumorigenic. (Author abstract) (23 Refs)

83. BIOCHEMICAL RESPONSE OF LYMPHOMA CELLS TO MITOGENIC STIMULATION BY PROLACTIN.

Richards JF, Beer CT, Bourgeault C, Chen K, Gout PW
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Mol Cell Endocrinol; 26(1/2):41-49 1982

The biochemical events involved in the mitogenic stimulation of cells by prolactin (PRL) at physiological concentrations were investigated in cultures of Nb 2 node rat lymphoma cells. After the addition of PRL (20 nanog/ml) at 18 hr to a stationary culture, cell numbers remained stable for approx 22 hr, then doubled. DNA synthesis remained low during the first 10 hr after addition of PRL, but rapidly increased to a peak at approx 17 hr. A second wave of DNA synthesis was then seen. Activity of ornithine decarboxylase (ODC) was measured in control cultures and cultures treated with PRL. Enzymatic activities of stationary cells was very low, while that of replicating cells was more than 100-fold higher. In the presence of PRL, ODC activity was substantially higher than that of cells growing in medium containing fetal calf serum. Addition of other pituitary hormones to stationary cultures had no effect on ODC activity, demonstrating that the increase in ODC activity was due to PRL per se. Addition of PRL resulted in striking increases of ODC and S-adenosyl methionine decarboxylase activities: each enzyme exhibited two peaks of activity, the second of which appeared to coincide with the increase in the rate of DNA synthesis. In the absence of PRL, cells accumulated early in the G1 phase, while PRL induced the cells to proceed through the cell cycle in a synchronized fashion. Thus, lymphoma cells are useful for studying biochemical events resulting from interaction of a mitogenic polypeptide hormone and its target cell. (24 Refs)

84. CONTROL OF CELL GROWTH BY TISSUE AND SERUM FACTORS.

Klein KJ
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Diss Abstr Int [B]; 42(11):4368-B 1982

KCl extracts from rat kidney, rat liver, and Morris hepatomas inhibited. 3H-thymidine incorporation into cultured cells. The most pronounced inhibition was achieved with the kidney extract. A normal serum protein disappears from the serum of animals bearing Morris hepatomas 7777 and 5123 as the tumors increase in size. Serum factor levels are increased well over those found in normal rats 24 hours after partial hepatectomy. Increased levels persist for 12 days following partial hepatectomy. The serum protein is also increased following injections of T3 (triiodothyronine) and is decreased in thyroidectomized animals. Elevated levels of T3 are correlated with elevated levels of the serum protein and both are correlated with increased hepatic DNA synthesis. Low levels of T3 as a result of thyroidectomy are followed by low levels of serum protein resulting in a diminished capacity for hepatic DNA synthesis and decreased hepatoma growth. T3 injections restored the capacity for hepatic DNA synthesis and hepatoma growth. Injection of purified serum factor into normal rats resulted in increased 3H-thymidine incorporation in liver cells. Hepatoma growth was higher in rats that had elevated serum factor levels at the time they received a hepatoma transplant. It is suggested that the synthesis of this serum protein is stimulated by T3 and hepatocyte proliferation and hepatoma growth are influenced by the serum protein. (no Refs)

EFFECTS OF ENDOGENOUS AND EXOGENOUS AGENTS ON NON-STEROID HORMONE ACTIVITY

85. EFFECTS OF RETINOIC ACID ON DIFFERENTIATION OF CHORIOCARCINOMA CELLS IN VITRO (MEETING ABSTRACT).

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Fed Proc; 41(3):683 1982

Choriocarcinoma cells secreted no immunoreactive pregnancy-specific beta 1-glycoprotein (PS betaG) in vitro. These cells can be induced to synthesize low levels of PS betaG by retinoic acid, 8-Bromo-cAMP (8BrcAMP), cholera toxin, methyl isobutyl xanthine (MIX), and 5-Bromo-2'-deoxyuridine (BrdUrd). Simultaneous addition of retinoic acid along with 8BrcAMP, cholera toxin, or MIX gave synergistic induction of PS betaG. Simultaneous addition of retinoic acid and BrdUrd failed to given even additive induction. In addition to stimulating PS betaG production, retinoic acid increased the production of human chorionic gonadotropin (hCG) and its alpha subunits (hCGalpha) by choriocarcinoma cells. Simultaneous addition of retinoic acid along with 8BrcAMP, cholera toxin, or MIX gave additive induction for hCG and hCGalpha. Passage of choriocarcinoma cells in medium containing retinoic acid induced a stable altered phenotype characterized by elevated levels of PS betaG, hCG, and hCGalpha. These retinoid-treated choriocarcinoma cells remained responsive to 8BrcAMP or compounds that increase intracellular cAMP concentrations and to BrdUrd: the production of PS betaG and hCG was greatly stimulated by 8BrcAMP, cholera toxin, or MIX and the production of hCG and hCGalpha was greatly inhibited by BrdUrd. However, the production of hCGalpha was only slightly induced by these cAMP modulators and the production of PS betaG was not increased by BrdUrd. Our data suggest that retinoic acid plus compounds that elevate cAMP concentration may induce differentiation of choriocarcinoma cells in vitro. (no Refs)

86. ENHANCEMENT OF HUMAN CHORIONIC GONADOTROPHIN PRODUCTION BY ANTIMETABOLITES.

Browne P, Bagshawe KD
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Br J Cancer; 46(1):22-29 1982

The action of methotrexate, actinomycin D, bleomycin, vincristine and hydroxyurea on the production of human chorionic gonadotrophin (hCG) by a choriocarcinoma cell line (BeWo) has been studied. hCG production per unit of cell protein was increased, and this was a continuing process only halted by cell death. The proportion of hCG-producing cells in the population increased from approx 5% to a max of approx 40% during incubation with vincristine. A possible explanation for these and related observations is that cytotoxic agents promote the differentiation of cytotrophoblast to syncytium. A similar mechanism could contribute to the unusual sensitivity of choriocarcinoma to cytotoxic agents. (Author abstract) (23 Refs)

87. EFFECTS OF A PROLACTIN- AND ADRENOCORTICOTROPIN-SECRETING TUMOR ON GONADOTROPIN LEVELS AND ACCESSORY SEX ORGAN WEIGHTS IN ADULT MALE RATS: A POSSIBLE ROLE OF THE ADRENALS.

Weber RF, Ooms MP, Vreeburg JT
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Endocrinology; 111(2):412-417 1982

The presence of the transplantable PRL- and ACTH-secreting tumor 7315a in intact male rats resulted in very high serum PRL levels, decreased levels of LH and FSH, and reduced weights of testes and accessory sex organs. In gonadectomized rats bearing a small testosterone-filled capsule, the tumor inhibited the postcastration rise in gonadotropins and reduced the weights of the prostate and seminal vesicles. However, after adrenalectomy of intact or gonadectomized male rats bearing a small testosterone-filled capsule, inhibitory effects of the tumor on serum gonadotropin levels or on reproductive organ weights were totally absent. These results show that in adrenalectomized male rats, hyperprolactinemia in itself does not affect gonadotropin secretion and the androgenic action of testosterone. Rather, the tumor might exert a gonadotropin inhibitory action through elevated levels of PRL combined with progesterone, which is secreted by the ACTH-stimulated adrenal. (Author abstract) (27 Refs)

88. ROLE OF ESTROGEN AND PROLACTIN IN THE GROWTH AND RECEPTOR LEVELS OF N-NITROSOMETHYLUREA-INDUCED RAT MAMMARY TUMORS.

Manni A, Rainieri J, Arafah BM, Finegan HM, Pearson OH
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Cancer Res; 42(9):3492-3495 1982

Forty-eight of 81 (59%) of N-nitrosomethylurea-induced rat mammary tumors regressed in av to almost one-half of the original size 10 days after ovariectomy (ovax) (hormone responsive), while 33 remained essentially unchanged (hormone resistant). At 20 days after ovax, further decline in hormone-responsive tumors was observed when the rats were treated daily with 0.9% NaCl soln on the 10th day after ovax. Treatment for the same length of time with estrogen either alone or in combination with bromocriptine (to effectively suppress serum prolactin level) prevented tumor regression in hormone-responsive tumors. A similar effect was observed when rats were treated with perphenazine (to stimulate endogenous prolactin secretion) either alone or in combination with the antiestrogen tamoxifen. Estrogen receptors (ERs) significantly declined after ovax. Treatment with estrogen or perphanazine did not have any significant effect on ER levels. Progesterone receptors (PGRs) became virtually undetectable after ovax. Treatments with estrogen, estrogen plus bromocriptine, and perphenazine plus tamoxifen but not perphenazine alone were able to partially restore PGRs although this effect was of borderline statistical significance. ER and PGR levels were not significantly different between hormone-responsive and -resistant tumors within each group. We conclude that both estrogen and prolactin play a role in the growth of the N-nitrosomethylurea-induced rat mammary tumor. Changes in ER and PGR levels did not correlate with tumor growth under the present experimental conditions. (Author abstract) (18 Refs)

89. LONG-TERM EFFECTS OF INTERNAL IRRADIATION OF ENDOCRINE SYSTEM IN FEMALE RATS.

Dedov VI
Inst. Advanced Training for Physicians, Moscow, USSR
Izv Akad Nauk SSSR [Biol]; (3):454-458 1982

The long-term effects of internal irradiation of the endocrine system were studied in random-bred female rats. The animals received single iv injection of 75Se-selenomethionine (SM: 1.22 x 10(4) becquerel/g). The absorbed doses were 50 rads in the whole body and in the ovaries and 100 rads in the pituitary gland, thyroid, and adrenals. Animals were sacrificed on day 2 of the diestrus 1 and 2 wk, 1, 3, 6, 9, 12, and 18 mo after SM administration. Prolonged internal irradiation induced permanent estrus in 60% of the female rats. The female rats with permanent estrus developed mammary gland neoplasms (the latent period of mammary gland tumors was 5.5-7 mo for mature rats and 2.5 mo for old rats), thyroid and adrenal adenomas, pituitary gland prolactinomas, and uterine polyps. Development of endocrine neoplasms was associated with SM-induced elevation of blood levels of estrogens and prolactin and deficiency of thyroxine. (13 Refs) (In RUS)

RECEPTOR/ BINDING SITES

90. MITOGENIC ACTIVITY OF INSULIN AND INSULIN-LIKE GROWTH FACTOR-II ARE MEDIATED BY THEIR RESPECTIVE RECEPTORS IN RAT HEPATOMA CELLS (MEETING ABSTRACT).

Massague J, Blinderman LA, Czech MP
University of Massachusetts Medical Center, Worcester, MA, 01605
Fed Proc; 41(3):496 1982

Covalent crosslinking of 125I-insulin, 125I-insulin-like growth factor I (IGF-I) and 125I-IGF-II to membranes from various tissues has allowed us to identify receptor structures for these three ligands. The insulin receptor is a disulfide-linked heterotetrameric complex that consists of two alpha subunits and two beta subunits. This receptor exhibits high affinity for insulin and a lower affinity for IGF-I and IGF-II. The IGF-I receptor has high affinity for IGF-I and low affinity for IGF-II and insulin, and is a Mr 350,000 disulfide-linked complex with a subunit structure similar to the insulin receptor. The labeled IGF-II receptor consists of a Mr 250,000 protein, and has a lower affinity for IGF-I than IGF-II. H-35 rat hepatoma cells exhibit insulin receptors with very low affinity for IGF-II, IGF-II receptors with no affinity for insulin, and no IGF-I receptors. Insulin stimulated DNA synthesis and increased the cell number in H-35 cultures growth arrested by serum starvation. Half maximal effects were achieved by 0.1nM insulin. 'Multiplication stimulating activity' (rat IGF-II) is also a potent mitogen for serum-starved H-35 cells. Half maximal effects were observed at 50-100pM rat IGF-II. The data suggest that both insulin and IGF-II can stimulate growth of H-35 hepatoma cells through their respective receptors. (no Refs)

91. ADENYLATE CYCLASE COUPLED BETA2-ADRENERGIC RECEPTORS IN A SMOOTH MUSCLE TUMOR CELL LINE (MEETING ABSTRACT).

Garmer J, Cornett LE, Norris JS
Departments of Medicine and Physiology, University of Arkansas for Medical Sciences, Little Rock, AR, 72205
Fed Proc; 41(3):1511 1982

The DDT1 MF-2 cell line was established by explantation from an androgen-estrogen induced leiomyosarcoma of the ductus deferens of a Syrian hamster. Since these cells morphologically resemble smooth muscle cells and contain alpha 1-adrenergic receptors, we chose to examine them for the presence of beta-adrenergic receptors. Binding of [3H]-dihydroalprenolol (DHA) to membranes of DDT1 cells grown in suspension culture was of high affinity, saturable, stereoselective and reversible. The dissociation constant for DHA was 0.8 nM with site number of 425 fmoles/mg protein. The order of agonist competition was isoproterenol greater than epinephrine greater than norepinephrine consistent with a beta 2-receptor interaction. Furthermore, Zinterol, beta 2-selective, was more effective than Metoprolol, beta 1-selective in competing for the DNA binding site. Also, the DDT1 cell beta 2-adrenergic receptor is functionally linked to adenylate cyclase as basal cyclic AMP accumulation (112pmol/10(6) cells/10') was stimulated by 10 uM isoproterenol (402pmol/10(6) cells/10'). Stimulation by isoproterenol was inhibited by 10uM propranolol (102pmol/10(6) cells/10'). In conclusion, the presence of both alpha 1-and beta 2-adrenergic receptors make the DDT1 cell an ideal model in which to study the actions of catecholamines on smooth muscle. (no Refs)

92. PHORBOL ESTERS MODULATE THE BINDING OF SEVERAL PEPTIDE HORMONES TO PITUITARY CELLS (MEETING ABSTRACT).

Osborne R, Tashjian AH
Department of Pharmacology, Harvard Medical School, Boston, MA
Toxicologist; 2(1):65 1982

Phorbol esters (PE) are potent tumor promoters which have been shown to alter specifically the binding of epidermal growth factor (EGF) to diverse cell types in culture. In GH4C1 cells, a clonal strain of rat pituitary cells, PE stimulate the synthesis and release of prolactin and inhibit growth hormone production after binding to specific PE receptors. GH4C1 cells also have specific membrane receptors for EGF, thyrotropin-releasing hormone (TRH), and somatostatin (SRIH). Treatment with PE decreased the binding of EGF, TRH and SRIH to GH4C1 cells. 12-O-Tetradecanoyl-13-phorbol acetate (TPA) at 100 ng/ml decreased 125I-EGF binding to 15% of control within 1 hr. By Scatchard analysis of 125I-EGF binding data, a 1-hr pretreatment with TPA decreased both the apparent affinity and the number of 125I-EGF receptors. After 4 hr of treatment, TPA decreased 3H-TRH binding to 35% of control due to a decrease in affinity with no change in the number of TRH receptors. After 24 hr, TPA also decreased 125I-Tyr1-SRIH binding to 40% of control. Effects of TPA on peptide binding were temperature dependent, occurring at 37 degrees but not 4C, and reversible. The potency order for decreased peptide binding was TPA greater than phorbol-12,13-didecanoate (PDD) greater than phorbol-12,13-dibenzoate, while phorbol and 4 alpha-PDD were inactive, which parallels the activity of these compounds as tumor promoters. Thus, unlike findings reported in certain other cells, the actions of PE on peptide ligand binding in GH4C1 cells were not specific for EGF. (no Refs)

OTHER RELATED STUDIES

93. A NEW VASOACTIVE PEPTIDE RELEASED FROM RAT PLASMA KININOGEN BY A RODENT TUMOR ACID PROTEASE (MEETING ABSTRACT).

Bedi GS, Balwierczak J, Back N
State University of New York at Buffalo, Buffalo, NY, 14260
Fed Proc; 41(3):1474 1982

This study reports on the purification and characterization of a new vasopeptide formed by the action of a Murphy-Sturm lymphosarcoma (MSLS) acid protease on rat plasma kininogen. Purified rat plasma kininogen (116 mg) was digested with 10 units of purified MSLS tumor acid protease in 0.05 M citrate-phosphate buffer, pH 3.0 for 16 hr. The released polypeptides were fractionated on Sephadex G-50 column. Smooth muscle stimulating activity was monitored on isolated rat uterus. The peptide purified further on a CM (carboxy methyl)-cellulose column showed a single ninhydrine positive spot (Mgly 2.1) on high voltage electrophoresis. Amino acid analysis revealed 2 Ser, 4 Pro, 1 Gly, 1 Ile, 1 Leu, 2 Phe and 2 Arg per M of peptide. The amino acid and carboxyl termini were identified as Ile and Leu respectively by dansyl chloride procedure and by treatment with carboxypeptidase Y. Tryptic and chymotryptic digestion products of polypeptide have been resolved by high voltage electrophoresis on thin-layer cellulose plates and complete sequence of these peptides is being elucidated. (no Refs)

94. INVESTIGATION OF THE ANORECTIC POTENCY OF CHOLECYSTOKININ IN TUMOR-BEARING RATS (MEETING ABSTRACT).

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Department of Surgery, University of Cincinnati Medical Center, Cincinnati, OH
Gastroenterology; 82(5,part2):1203 1982

We investigated whether the anoarectic effects of systemically-administered cholecystokinin (CCK) octapeptide would synergize with the anorexia elicited by two different lines of transplantable tumor. Since the intramuscular injection of 5x10(4) Walker 256 carcinosarcoma cells produces anorexia within 6 days and death by day 10 in immature Sprague-Dawley (S-D) rats, the anorectic effects of 0.5, 5.0 and 50 ug/kg (ip) of CKK of saline were tested 3, 5, 7 and 9 days after inoculation (32). Anorexia elicited by the same doses of CKK8 was also assessed in a more chronic model employing the sc injection of 2x10(6) methylcholanthrene-induced sarcoma cells in adult male Fischer (F) 344 rats. Since this tumor line typically yields anorexia by day 21 and death by day 40, CCK8 was tested on days 7, 14, 21, 28 and 35. Within each experiment the order of drug administration was determined by a Latin Square Design and equal numbers of nontumor-bearing rats served as controls. All rats were maintained on 16 hr food deprivation, with food intake being determined 1, 4 and 8 hrs after drug administration. Food intake was significantly reduced following the injection of CKK8 for 1 hr in F 344 rats and for 4 hrs in the S-D rats. Appropriate dose-response relationships were also observed, with larger doses of CKK inducing greater anorexia. No differential effect of CKK was observed in either line of tumor-bearing rats or at any time of tumor development. Thus, no synergism of CCK-induced anorexia with cancer anorexia was observed. These data do not support a role of CCK in mediating experimental cancer anorexia in rats. (no Refs)

95. HORMONAL CHANGES ASSOCIATED WITH HYPERTENSION IN NEOPLASIA-INDUCED HYPERCALCEMIA.

Sowers JR, Barrett JD
Endocrine Div., UCLA San Fernando Valley Program, Sepulveda Veterans Admin., Sepulveda, CA, 91343
Am J Physiol; 242(5):E330-E334 1982

Effects of hypercalcemia associated with a transplantable neoplastic tumor (Leydig cell tumor) on blood pressure and hormonal responses to immobilization stress were studied in rats. Development of hypercalcemia after tumor transplantation was associated with an elevation in blood pressure. Results suggested that elevated levels of the vasoactive hormones norepinephrine and angiotensin may play a role in development of hypertension in association with neoplasia-induced hypercalcemia. (30 Refs)

96. BIOLOGICAL CHARACTERIZATION OF THE C-1300 MURINE NEUROBLASTOMA: AN IN VIVO NEURAL CREST TUMOR MODEL.

Pons G, O'Dea RF, Mirkin BL
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Cancer Res; 42(9):3719-3723 1982

The C-1300 murine neuroblastoma has been biologically and biochemically characterized to determine its suitability as an in vivo neural crest tumor model for pharmacological studies. The tumor line was sustained in vivo by sc implantation of tissue segments or disaggregated tumor cells (10(6)/inoculum) into recipient A/J mice. Palpable tumors were initially detected 8.1 +-1.1 (SE) days after inoculation (n = 69). Daily tumor growth (estimated by transverse diameter) followed a Gompertzian-like growth curve. The survival time of implanted animals was 18.2 +-1.0 days after initial detection. Metastatic involvement of specific organs occurred with the following frequency: liver, 83%; kidney, 42%; and spleen, 29%. Biological specimens from control and tumor-implanted animals were assayed for catecholamines using high-pressure liquid chromatography coupled to an electrochemical detector. Dopamine and norepinephrine were present in the primary tumors, whereas no epinephrine was detected. In contrast, metastases obtained from the liver contained large concentrations of dopamine, norepinephrine, and epinephrine. The serum concentrations of dopamine and norepinephrine in tumor-bearing mice and the 24-hr urinary secretion of dopamine and norepinephrine were significantly greater than in non-tumor-bearing animals. This investigation has shown the in vivo C-1300 murine neuroblastoma to be a highly reproducible tumor model that is lethal, exhibits constant growth patterns, metastasizes, and secretes catecholamines. It should be useful to analyze the effects of chemotherapeutic agents upon in vivo tumor growth and to clarify their biochemical mechanisms of action. (Author abstract) (29 Refs)

97. THE EFFECT OF MEMBRANE FATTY ACID MODIFICATIONS ON DEPOLARIZATION-DEPENDENT EXOCYTOSIS IN THE CLONAL PHEOCHROMOCYTOMA CELL LINE, PC-12.

Williams TP
Georgetown University Medical Center, Washington, DC
Diss Abstr Int [B]; 42(9):3655-B 1982

The effect of changes in membrane lipid composition on the exocytotic release process was studied in the PC12 cells. None of the fatty acid modifications affected K+-stimulated release of 3H-norepinephrine. This observation indicated that the individual steps of the secretion process, including and subsequent to activation of membrane potential-dependent Ca++ channels were unaffected by the fatty acid changes. In contrast, both carbamylcholine and veratridine-stimulated exocytosis were diminished in cells enriched with unsaturated fatty acids. The diminished output of 3H-norepinephrine was observed at all concentrations of carbamylcholine and veratridine tested, with no change in the relative concentration-dependence. These results may have been due to a decrease in the number of receptors or ion channels, or due to a decrease in the ability of these membrane proteins to initiate ion fluxes. The decrease in carbamylcholine-stimulated release did not correlate with the simple presence of the fatty acids, but paralleled closely the time and concentration-dependent changes in phospholipid fatty acid composition. However, when oleate and arachidonate were simultaneously added to the culture medium, the inhibitory effects on carbamylcholine-stimulated release were additive, whereas the changes in phospholipid fatty acid composition were antagonistic. Thus, exposure of the PC12 cells to unsaturated fatty acids causes specific decreases in the activities of at least two stimulus/secretion processes. In addition, the decrease in receptor-mediated (carbamylcholine-stimulated) release was related to the concentration and time of exposure to the fatty acids, and it was reversible. However, the mechanism by which exogenous fatty acids produce these effects on release cannot be readily deduced from simple analysis of bulk membrane lipid composition. (no Refs)

98. CHARACTERIZATION OF SEROTONIN UPTAKE IN CULTURED PHEOCHROMOCYTOMA CELLS. COMPARISON WITH NOREPINEPHRINE UPTAKE.

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Mol Pharmacol; 21(2):368-373 1982

PC-12 cells were studied to find out whether they have an active uptake mechanism for 5-hydroxytryptamine (5-HT). The [3H]5-HT uptake at 37 C was concentration-dependent and exhibited Michaelis-Menten type kinetics. In the absence of external sodium the active uptake was reduced by 43-53%. The velocity of [3H]norepinephrine (NE) uptake at 37 C was concentration-dependent and exhibited saturation kinetics. The apparent Km of [3H]5-HT uptake was 0.39 uM, which was very similar to that reported for serotonergic neurons and platelets. The ability of iodoacetamide (5 milliM, mM), and 2,4-dinitrophenol (1 mM) to block the accumulation of [3H]5-HT and [3H]NE uptake indicated that the uptake occurred by active transport processes. [3H]NE uptake was blocked by ouabain (1 mM), but [3H]5-HT uptake was not affected. As expected, desmethylimipramine was more effective at blocking [3H]NE than [3H]5-HT uptake. The uptake of [3H]NE appeared to be more structurally specific as it was selectively inhibited by NE, whereas the uptake of [3H]5-HT was equally inhibited by both NE and 5-HT. Considerable inhibition of [3H]thymidine incorporation was observed after 30 and 90 min incubation with 6-hydroxydopamine. Equal cytotoxic effect was observed after 90 min of incubation with 5,6-dihydroxytryptamine. Results indicated that PC-12 cells can accumulate 5-HT from external medium by a non-saturable diffusion process and by high-affinity transport process. (32 Refs)

99. IDENTIFICATION OF CA++-CALMODULIN DEPENDENT ENZYME ACTIVITIES IN AN INSULIN-SECRETING TUMOUR.

Penn EJ, Hutton JC, Hales CN

Dept. Clinical Biochemistry, New Addenbrooke's Hosp., Hills Road, Cambridge CB2 2QR, England

Biochem Soc Trans; 10(4):266-267 1982

The nature of the major calmodulin-binding proteins was investigated in a transplantable rat islet-cell tumor. The eluted proteins, obtained by affinity chromatography from post-microsomal supernatant, representing 1% of the total tissue protein, were distributed among a large number of different peptides. The association between calmodulin and tumor proteins could be reversed by trifluoperazine and required Ca++ (but not Mg++). Investigation of the eluted protein fraction indicated the presence of myosin light-chain kinase, cyclic nucleotide phosphodiesterase, and phosphorylase kinase. Further investigation of myosin light-chain kinase activity indicated a relationship to enzyme from other previously described non-muscle and smooth muscle cells. The observation that insulin-secretory tissue contains myosin light-chain kinase activity, taken together with the previously reported presence of actin and myosin, is consistent with the involvement of Ca++-regulated contractile processes in the secretory mechanism. (19 Refs)

100. PLASMA GLUCOSE AND INSULIN CONCENTRATIONS AFTER IMPLANTATION AND SURGICAL RESECTION OF A TRANSPLANTABLE RAT INSULINOMA.

Flatt PR, Tan K, Bailey CJ, Swanston-Flatt SK, Marks V, Webster JD

Div. Nutrition, Univ. Surrey, Guildford, Surrey GU2 5XH, England

Biochem Soc Trans; 10(4):273-274 1982

Plasma glucose and insulin concentrations were determined after implantation and surgical resection of a transplantable rat insulinoma in NEDH rats. In one experiment small fragments of mature tumor from donor insulinoma-bearing rats were implanted sc in the subscapular region and blood samples were removed at various time from 6 days before, to 24 days after implantation. In a second experiment the implanted insulinomas were removed surgically and blood samples were removed before and at frequent intervals until 12 days after resection. The rats were observed for 60 days to check for recurrence of hypoglycemia. Implantation of tumor resulted in a progressive fall in glucose concentration, with development of hypoglycemia before the tumors were palpable and the establishment of hyperinsulinemia. Plasma insulin rose sharply after 17 days, with further fall in plasma glucose with death after 22-27 days. In contrast, surgical resection at day 21 resulted in a prompt and marked reversal of the metabolic abnormalities. Plasma insulin fell rapidly to the range for anesthetized controls within 10 min of operation. Hypoglycemia persisted for 60 min, followed by hyperglycemia for 1 day. While plasma glucose and insulin were normal 12 days after resection, tumor recurrence was seen in all rats, with resection giving a 20-60 day prolongation of life. The suitability of these rats as a tumor model for studies on the basic nature and properties of spontaneous insulinomas is discussed. (17 Refs)

101. PLASMA PROLACTIN (PRL) AND ITS METABOLIC CLEARANCE RATE (MCR) IN MALE AND FEMALE RATS FED 5 AND 20% DIETARY FATS (MEETING ABSTRACT).

Clinton SK, Mulloy AL, Visek WJ

University of Illinois, Urbana, IL, 61801

Fed Proc; 41(3):357 1982

It has been proposed that prolactin mediates the enhancement of mammary carcinogenesis by dietary fat. We have studied the effect of dietary fat level (10 and 40% of calories as corn oil) on plasma immunoreactive PRL and its MCR in male and female Sprague-Dawley rats. Rats were assigned to modified AIN diets at weaning. After 10 weeks, 15 rats per treatment were decapitated and trunk blood was assayed for PRL by radioimmunoassay. For the MCR studies 10 male and female rats per diet were anesthetized with pentobarbital, fitted with a jugular cannula and treated with 2-bromo-alpha-9 ergocryptine prior to receiving an exogenous bolus of PRL and collection of sequential blood samples to determine PRL clearance. There was no significant effect of fat on plasma PRL (ng/ml) in females at metestrus-diestrus [23 on low fat (LF) vs 17 on high fat (HF)] or proestrus-estrus [339 (LF) vs 329 (HF)]. There was also no significant difference in plasma PRL in male rats fed LF (39) vs those fed HF (55). Although male rats show a higher MCR than females there was no significant effect of fat. The MCR for males was .80 ml/min on LF and .76 mg/min on HF. The MCR for female rats was .36 and .42 respectively. The PRL and MCR data fail to show that dietary fat significantly changes the plasma PRL levels or its MCR. (no Refs)

102. AN ELECTROPHYSIOLOGICAL STUDY OF CULTURED HUMAN PITUITARY CELLS.

Dufy B, Israel JM, Zyzek E, Dufy-Barbe L, Guerin J, Fleury H, Vincent JD
Institut National de la Sante et de la Recherche Medicale, U 176, rue Camille Saint-Saens, 33077 Bordeaux Cedex, France
Mol Cell Endocrinol; 27(2):179-190 1982

Electrophysiological properties of human pituitary cells in culture are described and differences in the electrical properties of cultured human pituitary adenoma cells of different clinical pathology are discussed. Pituitary fragments removed from patients requiring selective transphenoidal adenectomy were studied histologically and hormones secreted by the cultures derived from the fragments were assayed. Tumor cells from acromegalic patients (AP) which released growth hormone (GH), prolactinomas which released large amounts of prolactin (PRL), a tumor which released ACTH and beta-endorphin, and 'non-functioning' (NF) pituitary tumors were cultured. Three different types of electrophysiological behavior were observed; 64% of the cells were not excitable either spontaneously or under depolarization, 27% were not spontaneously active but were excitable when depolarized, and 8.5% were spontaneously active. When 0.5 mM thyrotropin-releasing hormone (TRH) was directly ejected onto the cell being recorded, it depolarized cells cultured from pituitary fragments of AP and NF pituitary tumors (40% of the cells tested), but was ineffective on cells cultured from prolactinomas. Only cells cultured from NF tumors were sensitive to RU 24213, a strong agonist of dopaminergic receptors. When applied close to a firing cell, 10(-6) M RU 24213 induced a hyperpolarization associated with a strong decrease in the input resistance of the membrane. Gamma-aminobutyric acid-induced responses were recorded in 4 cells (31%) from GH-secreting tumors and in 10 cells (83%) from NF tumors. Only a slight hyperpolarization (2-5 millivolts) was observed in PRL-secreting cells. Results showed that human pituitary cells in culture are able to generate Ca++ dependent action potentials. (38 Refs)

103. RELATIONSHIPS BETWEEN STIMULATED PROLACTIN RELEASE FROM GH CELLS AND CYCLIC AMP DEGRADATION AND FORMATION.

Gautvik KM, Kriz M, Jahnsen T, Haug E, Hansson V
Fysiologisk Institutt, Universitetet i Oslo, Karl Johansgt. 47, Oslo 1, Norway
Mol Cell Endocrinol; 26(3):295-308 1982

The relationship between stimulated prolactin (PRL) release and formation and inactivation of cyclic AMP (cAMP) was studied in clonal strains (GH3 and GH4C1) of PRL producing rat-pituitary tumor cells (GH cells) after treatment with thyroliberin (TRH) and theophylline (TEP). The effect of TRH on adenyl cyclase activity in crude membrane fractions was investigated. Measurements of cAMP hydrolysis gave a non-linear Lineweaver-Burk plot. Changes in phosphodiesterase (PDE) activity caused by treatment with TRH and TEP were observed in the soluble fraction or in homogenates of cells. The enzymic activities in the soluble fraction and in the particulate fraction showed the same kinetics indicating the presence of identical or closely related cAMP PDEs. The maximal effect on PDE was observed at 30 nanomoles TRH. When TEP enhanced the release of PRL, the cells had increased cAMP concentrations and reduced cyclic nucleotide PDE activity. The effect of TRH on cAMP PDE was duplicated by treatment of the cells with high concentrations of cAMP. The effect of TRH on cAMP hydrolysis was dose-dependent, affecting the apparent maximal velocity of the enzyme rather than Km. Results indicated that TRH and TEP cause a rise in cellular concentrations of cAMP via different mechanisms. The highly positive correlation between PRL release and cellular cAMP concentrations support the notion that in GH cells, cAMP is a mediator of PRL release. (24 Refs)

104. ESTABLISHMENT AND CHARACTERIZATION OF A CONTINUOUS LUNG SQUAMOUS CELL CARCINOMA CELL LINE (U-1752).

Bergh J, Nilsson K, Zech L, Giovanella B
Wallenberg Lab., P.O. Box 562, S-751 22 Uppsala, Sweden
Anticancer Res; 1(6):317-322 1981

Establishment, biological characterization, and the cytogenetic analysis of a squamous carcinoma cell line (U-1752) from pleural effusion of a male with a pulmonary tumor preliminarily diagnosed as a poorly differentiated lung tumor of small cell type are described. The histopathological picture of sectioned tumor material obtained by bronchoscopy and mediastinoscopy was that of 'anaplastic' carcinoma. Most cells of the U-1752 line grew attached to the plastic. The nucleus of the monomorphic cells had 1-3 prominent nuclei, a moderate amount of cytoplasm, and resembled the explanted cells of the pleural effusion. The most conspicuous ultrastructural findings were numerous tonofilament-like fibers and desmosomes. Optimal growth of U-1752 was observed in F-10 medium containing 20% fetal calf serum. The population doubling time was 36 hr. After 3 wk growth in agarose, prominent colonies containing approx 25 cells were noted at a frequency of approx 1%. Progressive tumor growth was observed in 2/3 Swiss nude mice and in 4/4 NIH-2 nude mice from the first wk after inoculation. The anti-keratin antiserum revealed strong cytoplasmic fluorescence in U-1752 cells in the areas of cytoplasm where the tonofilaments were prevalent. One nanog/ml beta-human chorionic gonadotropin was excreted to the supernatant, corresponding to an av production rate of 5 x 10(-15) g/cell/72 hr. A total of seven metaphases were karyotyped. Chromosome number ranged from 48-71, with a modal number of 64. No special chromosome or chromosome region appeared to be preferentially involved in polyploidization or structural rearrangements. This studies clearly indicated the squamous cell nature of U-1752. (22 Refs)

105. UPTAKE OF HORSERADISH PEROXIDASE IN SPONTANEOUS ADENOMAS OF THE RAT PITUITARY (MEETING ABSTRACT).

Ilse G, Ryan N, Kovacs K
Department of Pathology, St. Michael's Hospital, University of Toronto, Toronto, Ontario M5B 1W8, Canada
Fed Proc; 41(3):336 1982

Horseradish peroxidase (HRP) was administered intravenously to 22 rats and its adenohypophysial uptake was studied by electron microscopy. Based on histology, immunocytology and electron microscopy, the adenohypophyses were divided into 3 groups: nontumorous, those with spontaneous prolactin cell adenomas or adenomas other than prolactinomas. There was a distinct difference in amount and location of HRP uptake between nontumorous adenohypophyses and adenomas. In nontumorous adenohypophyses, microbodies, noted mainly in growth hormone cells, contained HRP. Prolactin cells showed reaction product in Golgi complexes and endoplasmic reticulum. In prolactin cell adenomas, electron dense cells, large lysosomes and cytosegresomes were numerous; they took up HRP extensively. In adenomas other than prolactinomas, HRP was localized mostly on the basement membrane of cells. Macrophages, interspersed among adenoma cells, showed strong HRP activity. In nontumorous adenohypophyses, endothelial fenestrae showed HRP uptake whereas basement membrane of capillaries were negative. In prolactinomas, HRP deposits were noted on the thickened basement membrane of dilated capillaries. Nonprolactin cell adenomas exhibited extensive thickening of the capillary basement membrane with deposition of HRP. It can be concluded that pituitary adenoma cells retain the ability for endocytosis. (no Refs)

106. CHARACTERIZATION OF SEROTONIN UPTAKE IN CULTURED NEUROBLASTOMA CELLS. DIFFERENCE BETWEEN DIFFERENTIATED AND NONDIFFERENTIATED CELLS.

Yoffe JR, Borchardt RT
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Mol Pharmacol; 21(2):362-367 1982

Neuroblastoma cells clone N-2a was studied to find out whether the clone is a suitable model for the serotonergic neuron which could be used to investigate the mechanism by which 5,6-dihydroxytryptamine and 5,7-dihydroxytryptamine exert their neurotoxic effects. N-2a cells, differentiated by serum deprivation, accumulated serotonin by an active process. Results suggested that neuroblastoma cells clone N-2a might serve as a suitable model for serotonergic neurons. (45 Refs)

107. RADIOPROTECTIVE ACTIVITY OF SOME BETA-HYDROXYLATED INDOLE-ALKYLAMINES.

Deanovic Z, Trescec A, Kveder S, Iskric S, Supek Z
Dept. Biology, Rudjer Boskovic Inst., POB 1016, 41 001 Zagreb, Yugoslavia
Strahlentherapie; 158(6):375-377 1982

Chain beta-hydroxylated derivatives of tryptamine, 5-methoxytryptamine and 5-hydroxytryptamine (serotonin), respectively, were tested as radioprotectors in x-ray-irradiated mice. At midlethal dose of irradiation (725 cGy), tryptamine and serotonin protected all the animals, beta-hydroxylated tryptamine was only slightly less effective (survival 85%). On the contrary, when mice were irradiated with absolutely lethal dose (900 cGy), only beta-hydroxylated derivative of serotonin gave complete (100%) protection to the animals; 5-hydroxytryptamine and 5-methoxytryptamine protected about 90% of the animals. Beta-hydroxy-5-methoxytryptamine 35%, tryptamine 29%, whereas beta-hydroxytryptamine did not give any protection. (Author abstract) (10 Refs)

108. EFFECT OF ACTIVATORS OF CAMP ACCUMULATION ON VARIOUS STAGES OF GENOME EXPRESSION DURING ACUTE RADIATION INJURY. COMMUNICATION 3. COMPARATIVE ANALYSIS OF PROPERTIES OF RNA SYNTHESIZED IN ISOLATED NUCLEI OF LIVER AND SPLEEN FROM IRRADIATED RATS PRETREATED WITH SEROTONIN.

Tsudzevich BA, Galkina LA, Kucherenko NE
Biology Faculty, T. G. Shevchenko State Univ., Kiev, USSR
Radiobiologiia; 22(3):379-383 1982

The mechanism of radioprotective effect of serotonin was studied in cell nuclei isolated from the liver and spleen of irradiated rats subjected to whole-body irradiation with 800 rads. Fractionation of RNA synthesized in the isolated cell nuclei showed that irradiation inhibited the transcription, processing, and release of messenger RNA. Activation of cAMP system (pretreatment with serotonin) increased the radioresistance of RNA synthesis. (10 Refs) (In RUS)

109. INHIBITORY EFFECT OF SOMATOSTATIN ON BASAL AND VASOACTIVE INTESTINAL PEPTIDE-STIMULATED CYCLIC AMP PRODUCTION AND CYCLIC AMP-DEPENDENT PROTEIN KINASE ACTIVITY IN HELA CELLS.

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Departamento de Bioquimica, Facultad de Medicina, Alcala de Henares, Madrid, Spain
FEBS Lett; 144(1):173-176 1982

The effect of somatostatin (SST) on cyclic AMP (cAMP) production and cAMP-dependent protein kinase (PK) activity in HeLa cells was studied and the antagonistic relationship between vasoactive intestinal peptide (VIP) and SST on the regulation of cAMP and cAMP-dependent PK was investigated. VIP stimulated cAMP production in a dose-dependent manner. Half-maximal stimulation was observed at 2.5 +-0.3 nanoM (nM) VIP and maximal at greater than 10 nM. SST at 1 uM significantly inhibited basal and VIP-stimulated cAMP levels. Basal cAMP was inhibited by 40% at 1 uM SST whereas the increment produced by a maximally effective VIP concentration was reduced by 60%. The inhibitory effect of SST was dose-dependent. Both basal and VIP (30 nM)-stimulated cAMP production was progressively inhibited by increasing concentrations of SST, significant decreases being observed at 1 uM. A slight but significant effect on PK basal activity was observed; 1 uM SST inhibited by 60% the increase of the PK activity ratio elicited by 30 nM VIP. Results demonstrated that HeLA cells have specific receptors for SST, but it is not clear whether SST acts by first interacting with a membrane site or after penetrating into the cell. (24 Refs)

110. PURIFICATION AND PARTIAL CHARACTERIZATION OF A BONE-RESORPTIVE PROTEIN FROM CANCER ASCITES FLUID.

Humphries DE
Boston University Graduate School, Boston, MA
Diss Abstr Int [B]; 42(6):2341-B 1982

A protein capable of stimulating bone-resorption in vitro has been purified approximately 1250-fold from cancer ascites fluid. An apparent molecular weight of 43,000 daltons was calculated. In terms of its amino acid composition, the bone-resorptive protein is distinguished by its relatively high content of glycine (17%) and proline (11%). Initial biological characterization of the purified ascites protein demonstrated that the protein is as potent as parathyroid hormone in its ability to stimulate bone-resorption in vitro. Both proteins stimulated the release of radioactivity into the medium from bones which were previously labeled with calcium-45 or tritiated proline indicating that both matrix and mineral were solubilized. However, the bone-resorptive protein present in cancer ascites fluid can be distinguished from parathyroid hormone. The molecular weight of the protein purified in this study is approximately four times that of parathyroid hormone and the ascites protein contains no methionine while this amino acid is present in parathyroid hormone. Also, in contrast to parathyroid hormone, stimulation of isolated bone cells with the ascites protein did not increase cAMP levels. Moreover, although parathyroid hormone and the ascites protein increased calcium uptake in isolated bone cells, only the ascites bone-resorptive protein stimulated increased calcium uptake in isolated skin cells. (no Refs)

111. NON-HISTONE CHROMATIN PROTEIN METHYLATION IN NORMAL AND PROLIFERATING RAT LIVER AND IN HEPATOMA CELLS.

Kibert LG
University of Pittsburgh, Pittsburgh, PA, 15260
Diss Abstr Int [B]; 42(11):4271-B 1982

Non-histone chromatin protein methylation was examined in a number of proliferative model systems based on rat liver, as well as two transplantable Morris hepatomas. The study was aimed at determining whether alterations in methylation of these proteins might play a role in controlling liver and/or tumor cell proliferation. Methylation was estimated in vivo by injecting a double-labelled mixture of methionine (methyl-labelled 3H and internally labelled 14C) into the intact animal and calculating the ratios of incorporated radioactivity. Similar estimations were made in vitro using 3H methyl-labelled S-adenosyl methionine. Methylation of hepatic non-histone chromatin protein was found to be responsive to proliferative stimuli, insofar as these proteins acquired more radioactively labelled methyl groups in both in vivo and in vitro experiments. These observed increases occurred at specific times after the proliferative stimulus was administered; the vast majority of experiments employed either 70% hepatectomized or triiodothyronine injected animals. Higher-than-control-levels of nonhistone chromatin protein methylation appears also as a persistent characteristic in hepatoma tissues. The enhanced methylation appears, however, to be quantitative rather than qualitative in stimulated hepatic tissues: no causal link was established between this increased protein modification and hepatic cell proliferation per se. (no Refs)

112. EFFECT OF THYMOSIN FRACTION V ON LYMPHOBLASTS FROM BONE MARROW AND PERIPHERAL BLOOD OF NEWLY DIAGNOSED PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) (MEETING ABSTRACT).

Narula N, Miller DR, Good RA, Pahwa RN
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Fed Proc; 41(3):407 1982

Ficoll Hypaque separated lymphoblasts from bone marrow (BM) and peripheral blood (PB) from 24 patients with ALL (3 of T cell origin and 21 of Null cell type) were incubated with 25 ucg and 100 ucg of thymosin fr (fraction) V for 15 hours, washed and tested for induction of surface markers and T cell functions. Induction of receptors for peanut agglutinin (PNA) was noted in one sample and of sheep erythrocyte rosettes (ER) in 4. With monoclonal anti-Ia and anti-T cell (HuLyt 1, HuLyt 2 and HuLyt 3) antibodies, marked heterogeneity was noted in the expression of Ia and Lyt antigens on leukemic cells. Induction of one or more Lyt antigens was noted with thymosin fr V in 3 Null type of leukemic cell samples. Proliferative responses to mitogens phytohemagglutinin, concanavalin A and pokeweed were lacking in all samples and no change was noted after treatment of the cells with thymosin. Blasts from one patient were HuLyt 3 antigen (a pan-T cell marker) positive and ER negative, thereby indicating a dissociation between these two markers. This study indicates that T as well as Null cell leukemias, as defined by conventional tests, can potentially be subclassified on the bases of additional surface markers, and that thymosin fr V can induce certain T cell markers in some so-called 'null' type of leukemic cells. (no Refs)

113. ENDOCRINE SYSTEM IN THE OFFSPRING OF FEMALE RATS TREATED WITH 75SE-SELENOMETHIONINE.

Dedov VI, Norets TA
Res. Inst. Medical Radiology, Obninsk, USSR
Radiobiologiia; 22(3):409-412 1982

The state of the endocrine system was studied in the offspring of female random-bred rats subjected to a single iv administration of 75Se-selenomethionine (1.22 kilobecquerel/g) on day 11-13 of gestation. Prenatal exposure to radionuclide impaired the hormonal homeostasis and thus reduced the viability of the offspring (thyroid hypofunction in males, anovulatory estrus cycle in females, impairment of the functional state of the pituitary-adrenal system). By the age of 26 mo, 66% of males and 38% of females died, compared with 4% and 2.5%, respectively, in control. By the age of 24 mo all females with anovulatory cycle developed mammary gland tumors. Two females developed pituitary adenomas, four developed adrenal cortex tumors, three developed thyroid tumors, and four developed uterine polyps. It was concluded that the toxic effect of selenomethionine is associated with the deficiency of the hypothalamo-pituitary system that provides the release of the luteinizing hormone. (4 Refs) (In RUS)

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